PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Effects of head direction during prone position on postoperative delirium in elderly patients undergoing thoracolumbar spine surgery: a study protocol for a randomized controlled trial

Authors

zhu, jixiang; Chen, Yongzhuang; Chen, Yangyang; Ma , hong; liu, fengyun; chen, qian; Wang, Fang; chen, xuetai; Xue, Zhouya; ni, kun; Li, Feng; Qian, Bin

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Gibbison, Ben**
Affiliation	**University of Bristol**
Date	**25-Jan-2024**
COI	**None**

The manuscript needs to be copyedited into English. There are too many grammatical errors to pick up in a methodological review - but this will need to be done. This includes technical language in the inclusion and exclusion criteria. There is variation in the tenses - it should be in the future tense if it is a protocol that hasn't started!

Figure 1. We would usually expect an estimate of the number assessed for eligibility on the flow diagram so that we can decide what proportion of the population this represents (and therefore the generalisability).

The risk of delirium with the different head positions to calculate their sample size is not plausible. We are expected to believe that the incidence of delirium with the head in right position jumps from about 14% to 40%?? I think the authors need to come up with an informed incidence - I can't find why they have chosen 40% incidence for the right sided head tilt in any of the references they provide for this. (Reducing this will inflate their sample size).

I would usually expect to see a discussion in a protocol manuscript that covers why they chose what they did, strengths and limitations, what they hope it will add to the body of

literature, what the implications of the work are etc... The first 2 bullets of the S&L section are not strengths - they are simply stating what they are doing and therefore should be changed. The second 2 need some discussion around them and elaborating..

Reviewer	**2**
Name	**Weigeldt, Moritz**
Affiliation	**Charité Universitätsmedizin Berlin**
Date	**22-Feb-2024**
COI	**none**

To the Editor and Authors,

Thank you for the opportunity to review the manuscript “Effect of head direction during prone positioning on postoperative delirium in elderly patients underwent thoracolumbar spine surgery: study protocol for a pilot randomized controlled trial” which is being considered for publication in BMJ Open.

Postoperative delirium is an important issue and needs to be considered in perioperative care. This planned study will evaluate the influence of head rotation in the prone position during thoracolumbar spine surgery on postoperative delirium (POD). The authors describe a study that will put a lot of effort into extensive data collection at different time points, but there is little information on what they are trying to achieve with these data. The statistical section is vague, despite the use of Chi-Square’s or Fisher's exact test. The sample size calculation is also unclear. The authors refer to this study as a pilot study in the title and abstract, but did not give any information about this in the methods and the rest of the manuscript. The rationale for conducting this trial with this design is also not clear. These points, which I consider critical, are described in detail below:

1. Please give detailed information why so many co-authors were listed and which contribution will they have in this study?

2. In the introduction, you explain the clinical background of postoperative delirium (POD) and the effect of head rotation and reduced cerebral blood flow with appropriate references. However, there is no correlation between the incidence of POD and reduced cerebral blood flow described by the authors. On page 6, line 11, the authors refer to previous literature but do not provide any references.

The existing literature, especially that cited by the authors, mentions several risk factors, but none that link POD and reduced cerebral blood flow together. One risk factor that may be associated with reduced cerebral blood flow is hypotension, but this is controversial [1, 2]. On the other hand, hypertension is widely accepted in the literature as a risk factor for POD.

If, according to the title, this is a pilot study and you have hypothesised a correlation, please state this clearly throughout the manuscript.

1) Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth. 2020 Oct;125(4):492-504. doi: 10.1016/j.bja.2020.06.063. Epub 2020 Aug 11. PMID: 32798069.

2) Maheshwari K, Ahuja S, Khanna AK, Mao G, Perez-Protto S, Farag E, Turan A, Kurz A, Sessler DI. Association Between Perioperative Hypotension and Delirium in Postoperative Critically Ill Patients: A Retrospective Cohort Analysis. Anesth Analg. 2020 Mar;130(3):636-643. doi: 10.1213/ANE.0000000000004517. PMID: 31725024.

3. Page 6, line 32: What is meant by “Assessors are trained for homogenization”? Please explain.

4. Fig. is not informative at this early stage and should be omitted.

5. Page 8, line 58: What is the logic of adding fentanyl during anaesthesia “according to the concrete situation”, when remifentanil is continuously delivered during the entire anaesthesia?

6. Page 6, line 24ff: Here in the manuscript you described this study as a single-centre, single-blind, randomised controlled trial. In the title you have presented this as a pilot study, in the study registration the study is listed as a prospective study, please clarify your intentions.

7. Page 9, line 45ff: Your primary endpoint consists of different time points, please specify what you define as the prevalence of POD. A single positive test within 2-5 days after surgery at any time point?

8. Page 13, lines 10-11: “In this study, we suppose that right deviation of the head contributes to POD, compared with neutral and left deviation in a prone position” – What is the rationale to presume that the right deviation will elicit POD but not the left deviation?

The reference you provided [11, Master work of Liu YY] is not available, is there further evidence supporting this finding of a left-right difference head direction during prone positioning? Are there any other findings supporting this theory? Has a systematic search been conducted for existing evidence relevant to the research question, and how has this evidence been critically appraised and evaluated? The following study, for example, showed no difference between left and right positioning:

Andersen JD, Baake G, Wiis JT, Olsen KS. Effect of head rotation during surgery in the prone position on regional cerebral oxygen saturation: A prospective controlled study. Eur J Anaesthesiol. 2014 Feb;31(2):98-103. doi: 10.1097/EJA.0000000000000028. PMID: 24335413.

9. Page 13, line 7ff: in the section on sample size, the authors assume an incidence for POD (PR 40.5 %, PC 13.0 %, PL 14.5 %) according to the previous literature to which they refer to

[15-17], but this is not conclusive. One reference [16] is a meta-analysis that includes the first reference [15]. There is no information in the cited references on the positioning or rotation of the head in these patients, please explain the rationale for your assumed incidence of POD. Again, if you designed this as a pilot study as the title suggests, please make this clear throughout the manuscript and especially in the methods section. There are also no measures of feasibility and acceptability of the study protocol and intervention.

10. Statistics: You are using three groups (PR, PC, PL), why don't you correct the statistics for multiple testing? Please explain how you will deal with this issue.

Regarding the multiple secondary endpoints, have you considered using logistic regression analysis to identify independent risk factors that correlate with POD?

11. Page 10, line 17: what do you mean by resuscitation room? Operation theatre, recovery room, ICU/PACU?

12. Page 10, line 31: duplication of word points

13. Do you considered gender/sex considerations?

14. Did you use any reporting guidelines? What are your strategies for reducing the risk of bias?

The main problem with this study is that the relationship between head rotation and reduced cerebral blood flow is inconclusive, particularly assuming a difference between right and left deviation, the references are missing or not available, and the sample size analysis is also inconclusive because of the inadequate references. This will make it difficult to analyse the results when the trial is completed and will greatly affect the potential conclusions of the trial. A more detailed description of how the secondary endpoints will be handled in terms of statistical analysis will also greatly improve the study protocol.

If this is planned as a pilot study, this information is missing throughout the entire manuscript and especially in the methods section. The effort you have put into the extensive data collection without measuring the feasibility is also questionable and makes the classification as a pilot study unlikely or even pointless.

Reviewer **3**

Name **Khoshnood, Babak**

Affiliation **INSERM UMR 1153, Center for Epidemiology and Statistics, Sorbonne Paris Cité (CRESS), Paris Descartes University, Paris, France, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), DHU Risks in Pregnancy**

Date **15-Mar-2024**

COI **None.**

I was the statistical reviewer for this paper and my comments are limited to methods. The authors need to note how they will test for the success of randomization (balanced covariates) and in case of imbalance how covariate adjustment is to be made. Furthermore, the design includes repeated measures and no discussion of this aspect of the data are included (nested data) and how they will be analyzed - at least not explicitly. It was also unclear to me what the "hierarchical indicators" are and how the frequency distributions would be analyzed / interpreted.Finally, sample size calculations are not clearly described in terms of the longitudinal / repeated measures nature of the outcomes to be assessed.In general, the statistical section of the manuscript needs to be completed and revised.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Dr. Ben Gibbison, University of Bristol

Comments to the Author:
The manuscript needs to be copyedited into English. There are too many grammatical errors to pick up in a methodological review - but this will need to be done. This includes technical language in the inclusion and exclusion criteria. There is variation in the tenses - it should be in the future tense if it is a protocol that hasn't started!

Response: Thank you for your helpful suggestion. We have revised the manuscript to ensure consistency in future tense and have addressed grammatical errors and technical language issues. We sought assistance from a professional copyediting service, Editage. The revised version, marked with changes, has been uploaded as the “main document marked copy.”

Figure 1. We would usually expect an estimate of the number assessed for eligibility on the flow diagram so that we can decide what proportion of the population this represents (and therefore the generalisability).

Response: We appreciate your comments. We added the estimated number of participants assessed for eligibility to the flow diagram to provide a clearer understanding of the population representation and generalisability.

The risk of delirium with the different head positions to calculate their sample size is not plausible. We are expected to believe that the incidence of delirium with the head in right position jumps from about 14% to 40%?? I think the authors need to come up with an informed incidence - I can't find why they have chosen 40% incidence for the right sided head tilt in any of the references they provide for this. (Reducing this will inflate their sample size).

Response: Thank you for the valuable comment. We acknowledge that our previous study may have been premature in its assumptions. Epidemiological studies on postoperative delirium (POD) rarely address the impact of head direction during spinal surgery. In our preliminary experiments, we included a total of 32 patients (8 in the PC group and 24 in the PD group). Among these, one patient in the PC group and six in the PD group were diagnosed with POD.

Using these preliminary data, we calculated the sample size with a two-sided significance level of 0.05 and a power of 90%, resulting in a requirement of 200 patients per group. To account for an anticipated 20% loss to follow-up, we enrolled 500 patients in this study.

I would usually expect to see a discussion in a protocol manuscript that covers why they chose what they did, strengths and limitations, what they hope it will add to the body of literature, what the implications of the work are etc...

Response: Thank you for the insightful comment. We have now included a comprehensive discussion in the revised manuscript. This addition allowed us to reflect on our previous design choices, articulate the strengths and limitations of our study, and discuss the anticipated contributions to the existing body of literature.

The first 2 bullets of the S&L section are not strengths - they are simply stating what they are doing, and therefore, should be changed. The second 2 need some discussion around them and elaborating.

Response: Thank you for the suggestion. We have revised the first two points in the "Strengths and Limitations" section to better reflect the strengths of our study. Additionally, the last two points have been further elaborated on and discussed in detail in the concluding paragraph of the Discussion section.

Reviewer: 2
Dr. Moritz Weigeldt, Charité Universitätsmedizin Berlin
Comments to the Author:
The authors describe a study that will put a lot of effort into extensive data collection at different time points, but there is little information on what they are trying to achieve with these data. The statistical section is vague despite the use of Chi-Square's or Fisher's exact test. The sample size calculation is also unclear. The authors refer to this study as a pilot study in the title and abstract, but did not give any information about this in the methods and the rest of the manuscript. The rationale for conducting this trial with this design is also not clear. These points, which I consider critical, are described in detail below:

Response: Thank you for your professional and insightful comments. They have significantly helped us reconsider and refine our study design. We have addressed many of the issues and would greatly appreciate further constructive feedback. As this is our first paper on a study protocol, the experience has been highly rewarding, and we are grateful for your efforts.

1. Please give detailed information why so many co-authors were listed and which contribution will they have in this study?

Response: This being our first design of a clinical study protocol, we sought guidance from many co-authors who generously provided significant assistance. The contributions are as follows: Bin Qian took responsibility for the integrity of the work as a whole and served as the primary investigator. Jixiang Zhu, Yongzhuang Chen, Yangyang Chen, Kun Ni, Feng Li, and Bin Qian were involved in the study's design. Jixiang Zhu, Kun Ni, Feng Li, and Bin Qian drafted the manuscript. Yangyang Chen, Fengyun Liu, and Hong Ma contributed to the calculation of the sample size and provided statistical consultation. Qian Chen, Fang Wang, Xuetai Chen, and Zhouya Xue developed the case report forms and conducted a preliminary

trial. Jixiang Zhu, Yongzhuang Chen, Hong Ma, Qian Chen, Fang Wang, Zhouya Xue, Kun Ni, Feng Li, and Bin Qian were responsible for conducting the clinical trials. All authors contributed to revising the manuscript for important intellectual content. Jixiang Zhu, Yongzhuang Chen, and Yangyang Chen contributed equally to this study and are joint first authors.

2. In the introduction, you explain the clinical background of postoperative delirium (POD) and the effect of head rotation and reduced cerebral blood flow with appropriate references. However, there is no correlation between the incidence of POD and reduced cerebral blood flow described by the authors. On page 6, line 11, the authors refer to previous literature but do not provide any references. The existing literature, especially that cited by the authors, mentions several risk factors, but none that link POD and reduced cerebral blood flow together. One risk factor that may be associated with reduced cerebral blood flow is hypotension, but this is controversial [1, 2]. On the other hand, hypertension is widely accepted in the literature as a risk factor for POD. If, according to the title, this is a pilot study and you have hypothesised a correlation, please state this clearly throughout the manuscript.

1) Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth. 2020 Oct;125(4):492-504. doi: 10.1016/j.bja.2020.06.063. Epub 2020 Aug 11. PMID: 32798069.
2) Maheshwari K, Ahuja S, Khanna AK, Mao G, Perez-Protto S, Farag E, Turan A, Kurz A, Sessler DI. Association Between Perioperative Hypotension and Delirium in Postoperative Critically Ill Patients: A Retrospective Cohort Analysis. Anesth Analg. 2020 Mar;130(3):636-643. doi: 10.1213/ANE.0000000000004517. PMID: 31725024.

Response: Thank you for the insightful comments. We have made the following revisions:
1) Correlations between POD and cerebral blood flow: We have included the correlations between the incidence of POD and reduced cerebral blood flow in the second paragraph of the Introduction. Specifically, we have referenced studies that demonstrate a significant reduction in regional cerebral blood flow in patients with delirium, which affects both cortical and subcortical regions[1]. Additionally, improvements in cerebral blood flow have been observed in these regions following recovery from delirium[1].
2) Blood pressure and cerebral perfusion: We have expanded the discussion on blood pressure and cerebral perfusion in the second paragraph of the Discussion section. Reduced cerebral perfusion is associated with POD[2-4]. The middle cerebral artery mean flow velocity (MFV), as measured using transcranial Doppler, is a key marker for assessing cerebral perfusion[5]. Previous studies have shown that MFV and intracranial vertebral artery blood flow velocities decrease during head rotation in the prone position among young volunteers[6 7]. During cervical rotation, the MFV decreases by approximately 10%, and the jugular venous return is compromised[8]. Cerebral perfusion pressure, calculated as the difference between MAP and CVP (MAP - CVP), may be further impeded, even if blood pressure remains normal.
3) Correction of study design terminology: Our study is a randomised controlled trial. The use of “pilot” in the title and abstract was a clerical error and has been removed in the revised manuscript.

References:

1. Yokota H, Ogawa S, Kurokawa A, et al. Regional cerebral blood flow in delirium patients. *Psychiatry and clinical neurosciences* 2003;57(3):337-39.
2. Anderson BJ, Diamond JM. Under Pressure: Reduced Cerebral Perfusion as a Risk Factor for Postoperative Delirium in Lung Transplant Recipients. *Ann Am Thorac Soc* 2016;13(2):156-7. doi: 10.1513/AnnalsATS.201512-796ED

3. Ma H, Ahrens E, Wachtendorf LJ, et al. Intraoperative Use of Phenylephrine versus Ephedrine and Postoperative Delirium: A Multicenter Retrospective Cohort Study. *Anesthesiology* 2024;140(4):657-67. doi: 10.1097/aln.0000000000004774
4. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced Cerebral Perfusion Pressure during Lung Transplant Surgery Is Associated with Risk, Duration, and Severity of Postoperative Delirium. *Ann Am Thorac Soc* 2016;13(2):180-7. doi: 10.1513/AnnalsATS.201507-454OC
5. Soh S, Shim JK, Song JW, et al. Preoperative transcranial Doppler and cerebral oximetry as predictors of delirium following valvular heart surgery: a case-control study. *J Clin Monit Comput* 2020;34(4):715-23. doi: 10.1007/s10877-019-00385-x [published Online First: 20190903]
6. Mitchell JA. Changes in vertebral artery blood flow following normal rotation of the cervical spine. *Journal of Manipulative and Physiological Therapeutics* 2003;26(6):347-51. doi: 10.1016/s0161-4754(03)00074-5
7. Højlund J, Sandmand M, Sonne M, et al. Effect of head rotation on cerebral blood velocity in the prone position. *Anesthesiol Res Pract* 2012;2012:647258. doi: 10.1155/2012/647258 [published Online First: 2012/09/19]
8. Andersen JD, Baake G, Wiis JT, et al. Effect of head rotation during surgery in the prone position on regional cerebral oxygen saturation: A prospective controlled study. *Eur J Anaesthesiol* 2014;31(2):98-103. doi: 10.1097/eja.0000000000000028

3. Page 6, line 32: What is meant by "Assessors are trained for homogenization"? Please explain.

Response: We appreciate your comment. The phrase "Assessors are trained for homogenisation" refers to the standardised training provided to all assessors to ensure consistency in the interpretation and application of assessment scales. This training is designed to minimise potential variability in assessments that can arise from subjective interpretations by different assessors, thereby improving the reliability and accuracy of the data collected.

4. Fig. is not informative at this early stage and should be omitted.

Response: Thank you for your valuable suggestion. We have revised and updated the study flow chart.

5. Page 8, line 58: What is the logic of adding fentanyl during anaesthesia "according to the concrete situation", when remifentanil is continuously delivered during the entire anaesthesia?

Response: Fentanyl serves as our primary analgesic throughout the surgery. To prevent potential overdose and minimise the risk of postoperative nociceptive hypersensitivity, we will administer remifentanil in small, incremental doses to manage any minor analgesic deficiencies. This approach ensures effective and balanced pain control during the procedure.

6. Page 6, line 24ff: Here in the manuscript you described this study as a single-centre, single-blind, randomised controlled trial. In the title you have presented this as a pilot study, in the study registration the study is listed as a prospective study, please clarify your intentions.

Response: Thank you for bringing this to our attention. The study is designed as a single-center, single-blind, randomised controlled trial. The term "pilot" was a clerical error and has been removed from the revised manuscript.

7. Page 9, line 45ff: Your primary endpoint consists of different time points, **please specify what you define as the prevalence of POD**. A single positive test within 2-5 days after surgery at any time point?

Response: We appreciate your comment. In this study, we define the prevalence of POD as a positive test result at any time point within 5 days post-surgery.

8. Page 13, lines 10-11: "In this study, we suppose that right deviation of the head contributes to POD, compared with neutral and left deviation in a prone position" – What is the rationale to presume that the right deviation will elicit POD but not the left deviation?
The reference you provided [11, Master work of Liu YY] is not available, is there further evidence supporting this finding of a left-right difference head direction during prone positioning? Are there any other findings supporting this theory? Has a systematic search been conducted for existing evidence relevant to the research question, and how has this evidence been critically appraised and evaluated? The following study, for example, showed no difference between left and right positioning:
Andersen JD, Baake G, Wiis JT, Olsen KS. Effect of head rotation during surgery in the prone position on regional cerebral oxygen saturation: A prospective controlled study. Eur J Anaesthesiol. 2014 Feb;31(2):98-103. doi: 10.1097/EJA.0000000000000028. PMID: 24335413.

Response: Thank you for the comment.
1. Our initial hypothesis regarding the differential impact of right versus left head deviation on POD may have been premature. Preliminary experiments involving 24 patients (13 patients with head left deviated and 11 patients with head right deviated) in the PD group indicated 3 patients respectively were diagnosed with POD. Besides, 1 patient in the PC group (8 patients) were diagnosed with POD. Preliminary results from our study did not demonstrate a significant effect of right versus left head deviation on POD incidence. Instead, a difference on POD incidence was seen between PC group and PD group. Consequently, we have refined our hypothesis to suggest that maintaining the cervical spine in a neutral position may be associated with a lower incidence of POD compared to a deviated position.
2. We acknowledge the lack of evidence supporting the differential impact of head deviation on POD. Atherosclerosis, as measured by the Atherogenic Index of Plasma (AIP), can affect cerebral blood flow [9]. Both carotid and vertebral arteriosclerosis are manifestations of large-artery atherosclerosis. The left vertebral artery (LVA) tends to be more affected by atherosclerosis due to higher blood flow velocity and pressure compared to the right vertebral artery (RVA)[10]. For instance, a study reported that in healthy adults, the LVA is dominant in approximately 50% of the total population, the RVA in approximately 25%, and the remaining 25% of the total population[11]. Moreover, among 1,414 stroke-free participants with a mean age of ≥ 45 years, most (85%) had plaques in both carotid arteries. Notably, these plaques are more commonly found in the left carotid artery (67%) than in the right (33%)[12], and this difference was asymmetry between the left and right vessels. We plan to perform stratified analyses according to AIP and head deviation upon the completion of this study to explore these factors further.

References:

9. Huang Q, Liu Z, Wei M, et al. The atherogenic index of plasma and carotid atherosclerosis in a community population: a population-based cohort study in China. *Cardiovasc Diabetol* 2023;22(1):125. doi: 10.1186/s12933-023-01839-y [published Online First: 20230527]
10. Cagnie B, Barbaix E, Vinck E, et al. Atherosclerosis in the vertebral artery: an intrinsic risk factor in the

use of spinal manipulation? *Surg Radiol Anat* 2006;28(2):129-34. doi: 10.1007/s00276-005-0060-1 [published Online First: 20060324]
11. Cloud G, Markus H. Diagnosis and management of vertebral artery stenosis. *Qjm* 2003;96(1):27-54.
12. Selwaness M, van den Bouwhuijsen Q, van Onkelen RS, et al. Atherosclerotic Plaque in the Left Carotid Artery Is More Vulnerable Than in the Right. *Stroke* 2014;45(11):3226-30. doi: 10.1161/STROKEAHA.114.005202

9. Page 13, line 7ff: in the section on sample size, the authors assume an incidence for POD (PR 40.5 %, PC 13.0 %, PL 14.5 %) according to the previous literature to which they refer to [15-17], but this is not conclusive. One reference [16] is a meta-analysis that includes the first reference [15]. There is no information in the cited references on the positioning or rotation of the head in these patients, please explain the rationale for your assumed incidence of POD. Again, if you designed this as a pilot study as the title suggests, please make this clear throughout the manuscript and especially in the methods section. There are also no measures of feasibility and acceptability of the study protocol and intervention.

Response: We appreciate your comments. We acknowledge that our earlier statement may have been made prematurely. Epidemiological studies on POD rarely report the impact of head direction during spine surgeries. Our preliminary study included a total of 32 patients (8 in the PC group and 24 in the PD group). Among them, only one had POD in the PC group and six in the PD group. To achieve a power of 90% with a two-sided significance level of 0.05, the required sample size was calculated to be 200 patients per group. However, to account for an anticipated 20% loss to follow-up, a total of 500 patients will be enrolled.

10. Statistics: You are using three groups (PR, PC, PL), why don't you correct the statistics for multiple testing? Please explain how you will deal with this issue. Regarding the multiple secondary endpoints, have you considered using logistic regression analysis to identify independent risk factors that correlate with POD?

Response: Thank you for your helpful comments. A total of 32 patients (8 in the PC group and 24 in the PD group) were included in our preliminary experiments. Of these, only one patient was diagnosed with POD in the PC group and six in the PD group. However, these findings did not show any significant effect of head lateralization on POD. Consequently, we have refined our hypothesis to focus on whether maintaining the cervical spine in a neutral position results in a lower incidence of POD compared to a deviated position.

11. Page 10, line 17: what do you mean by resuscitation room? Operation theatre, recovery room, ICU/PACU?

Response: Thank you for bringing this to our attention. The term “resuscitation room” referred to the Post-Anesthesia Care Unit (PACU). We have corrected the description to accurately reflect this in the revised manuscript.

12. Page 10, line 31: duplication of word points

Response: We appreciate your comment. We have removed the duplicated words to correct the error.

13. Do you considered gender/sex considerations?

Response: We appreciate your inquiry. We have considered gender differences, as reported in the literature, which indicate variations in vertebral artery blood flow during different head positions[6]. Specifically, a mild reduction in blood flow was observed in males but not in females during ipsilateral rotation[6]. Therefore, gender will be included as a factor in our stratified analyses to ensure a comprehensive evaluation of its impact on POD.

Reference:

6. Mitchell JA. Changes in vertebral artery blood flow following normal rotation of the cervical spine. *Journal of Manipulative and Physiological Therapeutics* 2003;26(6):347-51. doi: 10.1016/s0161-4754(03)00074-5

14. Did you use any reporting guidelines? What are your strategies for reducing the risk of bias?

Response: We appreciate your comment. We have adhered to reporting guidelines, specifically the SPIRIT guidelines for protocol design. Additionally, we will refer to the consensus statement and other relevant guidelines to mitigate the risk of bias [13].

Reference:

13. Hughes CG, Boncyk CS, Culley DJ, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention. *Anesth Analg* 2020;130(6):1572-90. doi: 10.1213/ane.0000000000004641

The main problem with this study is that the relationship between head rotation and reduced cerebral blood flow is inconclusive, particularly assuming a difference between right and left deviation, the references are missing or not available, and the sample size analysis is also inconclusive because of the inadequate references. This will make it difficult to analyse the results when the trial is completed and will greatly affect the potential conclusions of the trial. A more detailed description of how the secondary endpoints will be handled in terms of statistical analysis will also greatly improve the study protocol.

If this is planned as a pilot study, this information is missing throughout the entire manuscript and especially in the methods section. The effort you have put into the extensive data collection without measuring the feasibility is also questionable and makes the classification as a pilot study unlikely or even pointless.

Response: Thank you for your insightful comment. We acknowledge the concerns raised regarding the relationship between head rotation and cerebral blood flow, the need for more robust references, and the clarity of our sample size analysis. We understand that these factors are critical for interpreting the results and drawing reliable conclusions. We have revised the resubmitted manuscript to reflect these changes.

Reviewer: 3

Dr. Babak Khoshnood, INSERM UMR 1153, Center for Epidemiology and Statistics, Sorbonne Paris Cité (CRESS), Paris Descartes University, Paris, France

Comments to the Author:

I was the statistical reviewer for this paper and my comments are limited to methods. The authors need to note how they will test for the success of randomization (balanced covariates) and in case of imbalance how covariate adjustment is to be made. Furthermore, the design includes repeated measures and no discussion of this aspect of the data are included (nested data) and how they will be analyzed - at least not explicitly. It was also unclear to me what the "hierarchical indicators" are and how the frequency distributions would be analyzed / interpreted. Finally, sample size calculations are not clearly described in terms of the

longitudinal / repeated measures nature of the outcomes to be assessed.In general, the statistical section of the manuscript needs to be completed and revised.

Response: Thank you for your valuable comment. We have revised the statistical section of the manuscript as follows:
Statistical analyses will be conducted using SPSS version 20.0. Data will be presented as mean ± standard deviation (SD) for normally distributed data and median (interquartile range) for non-normally distributed data. Comparisons will be made using independent-sample t-tests for normally distributed data and Mann–Whitney U-tests for non-normally distributed data. Categorical data will be expressed as numbers or percentages and analysed using Fisher's exact test or chi-squared tests. Univariate repeated measures analysis of variance (ANOVA) will be used for intragroup comparisons, with post hoc tests and Bonferroni correction applied to control for Type I errors. A Mantel–Haenszel test, stratified by potential influencing factors such as age (youngest-old [65–74 years], middle-old [75–84 years], oldest-old [> 85 years]), AIP, gender (male and female), and head deviation (left or right), will be used to compare the risk of POD between groups. Statistical significance will be set at $P < 0.05$.

1. Yokota H, Ogawa S, Kurokawa A, et al. Regional cerebral blood flow in delirium patients. *Psychiatry and clinical neurosciences* 2003;57(3):337-39.
2. Anderson BJ, Diamond JM. Under Pressure: Reduced Cerebral Perfusion as a Risk Factor for Postoperative Delirium in Lung Transplant Recipients. *Ann Am Thorac Soc* 2016;13(2):156-7. doi: 10.1513/AnnalsATS.201512-796ED
3. Ma H, Ahrens E, Wachtendorf LJ, et al. Intraoperative Use of Phenylephrine versus Ephedrine and Postoperative Delirium: A Multicenter Retrospective Cohort Study. *Anesthesiology* 2024;140(4):657-67. doi: 10.1097/aln.0000000000004774
4. Smith PJ, Blumenthal JA, Hoffman BM, et al. Reduced Cerebral Perfusion Pressure during Lung Transplant Surgery Is Associated with Risk, Duration, and Severity of Postoperative Delirium. *Ann Am Thorac Soc* 2016;13(2):180-7. doi: 10.1513/AnnalsATS.201507-454OC
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VERSION 2 - REVIEW

Reviewer	**1**
Name	**Gibbison, Ben**
Affiliation	**University of Bristol**
Date	**27-Aug-2024**
COI	**None**

The 3D-CAM cannot give you the severity of delirium - merely a classification of whether or not it is present.

The sample size section is now even smaller, so that I cannot see what their promotion of delirium they expect, what reduction they expect.

I could not see a flow diagram with any number of eligible patients for assessment on it still (even in the additional files).

Discussion - all risks quoted are relative risks (e.g. 4-5 times increase). Need absolute risks - 4-5 x times increase in a small number, is still a small number!!

Reviewer	**2**
Name	**Weigeldt, Moritz**
Affiliation	**Charité Universitätsmedizin Berlin**
Date	**10-Sep-2024**
COI	**none**

Dear Authors,

I appreciate the effort you put into revising the manuscript, the comments were addressed satisfactorily. As you changed your sample size and the derivation of the study question, the number of potential participants increased. Overall, your study protocol is now adequate and appropriate for publication. One note: Do you need to submit an ethics amendment because of the major changes in the study?

Reviewer	**3**
Name	**Khoshnood, Babak**

Affiliation **INSERM UMR 1153, Center for Epidemiology and Statistics, Sorbonne Paris Cité (CRESS), Paris Descartes University, Paris, France, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), DHU Risks in Pregnancy**

Date **15-Oct-2024**

COI **None.**

Thank you for addressing my questions and comments. Just one minor additional suggestion: Use past tense instead of future tense when you describe the statistical analysis you have done. After all, you have done them already!

VERSION 2 - AUTHOR RESPONSE

Reviewer: 1
Dr. Ben Gibbison, University of Bristol
Comments to the Author:
The 3D-CAM cannot give you the severity of delirium - merely a classification of whether or not it is present.

Response: We appreciate your detailed commentary. 3D-CAM will be used to assess the incidence of POD, and the severity of POD will be assessed by the Memorial Delirium Assessment Scale (MDAS). We have corrected the potentially ambiguous descriptions in the *Postoperative assessments* section.

The sample size section is now even smaller, so that I cannot see what their promotion of delirium they expect, what reduction they expect.

Response: We sincerely appreciate your valuable feedback. Our primary aim is to determine whether maintaining a neutral cervical spine position results in a lower incidence of POD compared to a deviated position. Due to changes of our study question, we recalculated the number of potential participants based on our preliminary experiments. Given the bias associated with the small sample size in the preliminary study, we will conduct an interim analysis once the sample size reaches half of the calculated total to further refine our sample size.

I could not see a flow diagram with any number of eligible patients for assessment on it still (even in the additional files).

Response: We appreciate your kind reminder and acknowledge our previous oversight regarding the flow diagram. The numbers of eligible patients for assessment have now been included.

Discussion - all risks quoted are relative risks (e.g. 4-5 times increase). Need absolute risks - 4-5 x times increase in a small number, is still a small number!!

Response: Thank you for the exact suggestion. We have replaced vague descriptions with precise ones in the first paragraph of the *Discussion* section.

Reviewer: 2

Dr. Moritz Weigeldt, Charité Universitätsmedizin Berlin

Comments to the Author:

Dear Authors,

I appreciate the effort you put into revising the manuscript, the comments were addressed satisfactorily. As you changed your sample size and the derivation of the study question, the number of potential participants increased. Overall, your study protocol is now adequate and appropriate for publication. One note: Do you need to submit an ethics amendment because of the major changes in the study?

Response: We appreciate your insightful comments. The ethics amendment has been approved by the ethics examination committee, and the new ethical approval number has been updated in the *Ethics and Dissemination* section. Additionally, the registration information has been revised in the *Chinese Clinical Trial Registry*.

Reviewer: 3

Dr. Babak Khoshnood, INSERM UMR 1153, Center for Epidemiology and Statistics, Sorbonne Paris Cité (CRESS), Paris Descartes University, Paris, France

Comments to the Author:

Thank you for addressing my questions and comments. Just one minor additional suggestion: Use past tense instead of future tense when you describe the statistical analysis you have done. After all, you have done them already!

Response: We appreciate your helpful suggestion. We have checked the tense in the *Sample size* section.

VERSION 3 - REVIEW

Reviewer	**2**
Name	**Weigeldt, Moritz**
Affiliation	**Charité Universitätsmedizin Berlin**
Date	**11-Nov-2024**
COI	

Thank you for addressing my questions and comments. Overall, your study protocol is now adequate and appropriate for publication.