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)

Impact of noradrenaline versus phenylephrine on brain circulation, organ blood flow and tissue oxygenation in anesthetized patients with brain tumours: study protocol for a randomized controlled trial.

Authors

Faisal Mohamad, Niwar; Koch, Klaus Ulrik; Aanerud, Joel; Meier, Kaare; Mikkelsen, Irene Klærke; Espelund, Ulrick S.; Eriksen, Christian Fenger; Juul, Niels; Alstrup, Karen Baden; Jespersen, Bo; Fries, Lene Marie; Tankisi, Alp; Dyrskog, Stig; Cortnum, Søren Ole Stigaard; Sindby, Ann Katrine; Borghammer, Per; Tolbod, Lars Poulsen; Meng, LingZhong; Korshoej, Anders Rosendal; Rasmussen, Mads

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Wiberg, Sebastian**
Affiliation	**Rigshospitalet, Department of Cardiology**
Date	**29-Nov-2024**
COI	**None**

The authors Niwar Mohamad and collegues present a protocol for a randomized trial to investigate the impact of norepinephrine versus phenylephrine on brain circulation, organ blood flow and tissue oxygenation in anesthetized patients with brain tumours.

I would like to congratulate the authors on a well-written protocol on an exciting and well-designed trial.

Given that the trial is currently enrolling patients, I will not provide any fundamental suggestions regarding the trial design but only provide a few minor comments:

- I do not quite understand the sample size calculation. The way I read it, a total of 32 patients are needed to achieve a power of 0.8 at an alpha of 0.05 give a between-group difference of 3,8ml.... In the same sentence you write that a drop-out rate of 20% still results in a power of 0.8.

- In the ethics section, you describe risks of prolonged anaesthesia but do not address other potential risks. Is repeated PET associated with additional risks? If so, it should likely be described.

I look forward to reading the results of the trial.

Reviewer	**2**
Name	**Huang, Han**
Affiliation	**Sichuan University West China Second University Hospital, Department of Anesthesiology**
Date	**17-Jan-2025**
COI	**None**

This is an interesting research protocol and I am looking forward to see the final results.

There are two minor concerns from me,

1. the included patients diagnosed with "supratentorial brain tumours", which is kind of beyond my expertise. How are these kind of patients different from normal patients in brain perfusion? In other words, can the results from this trial be extrapolated into patients without brain tumors?

2. PET2 scanning was performed while the patients were anesthetized. How will the haemodynamical parameters be maintained during this period. I guess hypotension will not be uncommon during this phase, which would change the perfusion to brain and other vital organs.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Dr. Sebastian Wiberg, Rigshospitalet

Comments to the Author:

The authors Niwar Mohamad and collegues present a protocol for a randomized trial to investigate the impact of norepinephrine versus phenylephrine on brain circulation, organ blood flow and tissue oxygenation in anesthetized patients with brain tumours.

I would like to congratulate the authors on a well-written protocol on an exciting and well-designed trial. We thank the reviewer for this comment.

Given that the trial is currently enrolling patients, I will not provide any fundamental suggestions regarding the trial design but only provide a few minor comments:

- I do not quite understand the sample size calculation. The way I read it, a total of 32

patients are needed to achieve a power of 0.8 at an alpha of 0.05 give a between-group difference of 3,8ml.... In the same sentence you write that a drop-out rate of 20% still results in a power of 0.8.
Answer: The reviewer is correct. Accordingly, we have edited the text. It now reads "Given a between-group difference in CBF = 3,8 ml/100g/min in favour of the noradrenaline group a significance level of 0.05 and a power of 80%, the study requires 15 patients in each group to detect a significant difference in CBF changes between the two vasopressors. Considering a possible dropout rate of 6%, and to increase the comparability of the two groups, we decided to recruit a total of 32 patients, with 16 patients in each arm. See 'Sample size and statistical analysis' section.

- In the ethics section, you describe risks of prolonged anaesthesia but do not address other potential risks. Is repeated PET associated with additional risks? If so, it should likely be described.
Answer: In the 'Methods' section we have specified the dosimetry of the study. The total radiation dose per patient is 5.88 mSv. This dosage is within the acceptable limits as defined by the Danish Ethics Committee. In the ethics section (page 13) we have added that we "do not find that the prolonged period of general anaesthesia nor the PET radiation dose (see Methods section) will pose significant additional risk to the patient"

I look forward to reading the results of the trial.

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Reviewer: 2

Prof. Han Huang, Sichuan University West China Second University Hospital

Comments to the Author:

This is an interesting research protocol and I am looking forward to see the final results. There are two minor concerns from me,

1. the included patients diagnosed with "supratentorial brain tumours", which is kind of beyond my expertise. How are these kind of patients different from normal patients in brain perfusion? In other words, can the results from this trial be extrapolated into patients without brain tumors?
ANSWER: The presence of a brain tumour and associated edema can impact cerebral perfusion due to mass effect, increased intracranial pressure, and vascular compression, primarily affecting the ipsilateral hemisphere. Consequently, changes in flow and metabolism observed in the contralateral hemisphere may to some extent reflect physiology seen in individuals without brain pathology. However, confirming these findings in a cohort without neurological disease is necessary. Additionally, brain tumour patients exhibit pathophysiological similarities with those suffering from traumatic brain injury, subarachnoid haemorrhage, and intracerebral haemorrhage. Therefore, our results may be applicable to these patient groups. We have not added or edited in the manuscript in response to this question.

2. PET2 scanning was performed while the patients were anesthetized. How will the haemodynamical parameters be maintained during this period. I guess hypotension will not be uncommon during this phase, which would change the perfusion to brain and other vital organs.

ANSWER: The reviewer is correct. This is the most delicate part of the protocol. Accordingly we are very careful when we induce the patients. We have added the following sentence in the methods section describing the experimental protocol and intervention**:** "To avoid significant hypotension after anaesthesia induction, a carefully balanced anaesthesia induction is used, including administration of a crystalloid fluid bolus and if necessary atropine"

Reviewer: 1

If you have selected 'Yes' above, please provide details of any competing interests.: Not applicable

Reviewer: 2

If you have selected 'Yes' above, please provide details of any competing interests.: Not applicable