PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of ephedrine and phenylephrine on brain oxygenation and microcirculation in anesthetized patients with cerebral tumors: study protocol for a randomized controlled trial.
AUTHORS	Koch, Klaus; Tietze, Anna; Aanerud, Joel; Öettingen, Gorm; Juul, Niels; Sørensen, Jens Christian; Nikolajsen, Lone; Østergaard, Leif; Rasmussen, Mads

VERSION 1 – REVIEW

REVIEWER	Christian Dualé CPC-CIC CHU de Clermont-Ferrand France
REVIEW RETURNED	13-Jul-2017

GENERAL COMMENTS	This is the protocol of a randomised controlled trial (RCT) comparing the cerebral effects of two vasopressors currently used in anaesthesia, ephedrine and phenylephrine on cerebral oxygenation and microcirculation in anaesthetised patients with cerebral tumours. The study has started in September 2015 and is registered on ClinicalTrials.gov under the reference NCT02713087. This trial aims at responding to a relevant clinical issue, while there are many data to support a better tolerance of ephedrine, probably due to its dual effect (vasoconstriction + improvement of cardiac output), while phenylephrine, by a sole vasoconstriction, might be deleterious under particular conditions. All the hypotheses and the history of previous research are given in the following articles comparing the two drugs, in which cerebral oxygenation (SctO2) was assessed by near-infrared spectroscopy (NIRSS): - with vasopressors administered as boluses to treat hypotension in female patients with a low vascular risk. [1]; - with vasopressors administered as an infusion to prevent hypotension during caesarean section under spinal anaesthesia, [2]; - with vasopressors administered as boluses to treat hypotension in patients undergoing various surgeries, anaesthetised with propofol and remifentanil (BIS- but not target-controlled) [3]; - with vasopressors administered as boluses to treat the first occurring hypotension in patients carotid endarterectomy [4,5]: note that in the second study, which was a RCT, the advantages of ephedrine were quite mild however. The current study adds information to the available data, as this is not an indirect assessment of cerebral oxygenation, but a complete intra-tissular exploration, in a surgical model still not studied. The

	authors clearly focus – as they state in their introduction and in their declaration on ClinicalTrials.gov – that their primary outcome shall be the capillary transit-time heterogeneity (CTH), to be measured either by magnetic resonance imaging (MRI) or by positron emission tomography (PET), in two separated sub-studies. As I am not a specialist, neither of MRI, nor PET, my comments will focus on the other aspects of the protocol. The way anaesthesia is conducted is correct, and the standardisation is properly done. This is an important point in such studies in which both groups have to be well controlled. The randomisation is conducted with rather big blocks (of 12), while there are two studies of 12 vs. 12: what is done is done, I just hope there will not be bad surprises at the end… There is few information about the blinding, but I believe that, if the MRI/PET parameters were measured unaware of the treatment given (which is easy to do), this would be a quasi-double-blind study, as the patient can be easily blinded. What was exactly planned? My first big concern is about the clinical relevance. The authors state that vasopressors “are commonly used during brain tumour surgery to maintain sufficient cerebral perfusion pressure (CPP) in order to ensure adequate cerebral oxygenation”, but the reference given to support this relates only to traumatic brain injury (Bratton SL et al., ref n°1). This must justify the protocol, in which patients had an intravenous infusion of either ephedrine (2mg/ml) or phenylephrine (0.1mg/ml) “until main arterial blood pressure (MABP) increases to above 60 mmHg, or by 20% relative to the baseline”. I can admit that a good cerebral perfusion is always preferable in surgeries at risk of damaging brain, but does this justify a systematic infusion of vasopressors, furthermore to induce a mild hypertension, rather than a normotension? At this point (as the study is already initiated), the authors have these options: - either to provide published recommendations to justify a mild hypertension in such surgeries; - or to admit that the vasopressors were not administered for what they are currently indicated (intraoperative hypotension), so the pharmacological conditions are not exactly these of the clinical practice, and the results should be interpreted with caution; - a third possibility would be if the so called “baseline” (which is actually “the first MABP measured at the time of the initial MRI or PET sequence”) was actually an hypotensive condition: in this case, the conditions of administration would be correct, but with ethical concerns (the treatment should have been given earlier…). My second big concern is about the sample size calculation. The current manuscript states that the primary endpoints are “between-groups absolute and relative differences in CBF, CBV, MTT, CTH and calculated and measured CMRO2 and OEF respectively”. This is not correct (as there would be 14 outcomes), and not in accordance to the declaration on ClinicalTrials.gov, in which only the CTH (I suppose, its absolute value for each sub-study) is declared as the primary outcome. So let us consider that CTH is the primary outcome, and read now the sample size calculation:

	- the type-I and type-II errors are good, but was the hypothesis bilateral? - the expected effect size is a “10% increase in CTH giving infusion phenylephrine compared to ephedrine”: must we understand that there will be a 10%-increase of CTH under phenylephrine, vs. a 0%-increase under ephedrine, or a difference of 10% between groups, but 10% of what ? - to what refers the “difference in mean of 0.3216 ± 0.2”, I do not see anything like that in the two given references (Rasmussen M et al., 2010, n°26; Rasmussen M et al., 2004, n°27). I must remind that the following information must clearly given (in addition to the type-I and type-II errors): - the predefined primary outcome (e.g. the CTH, or the effect of the drug on the CTH, expressed as a percentage/rate of the pre-treatment value); - the hypothesis (unilateral or bilateral; bilateral is preferable in a pilot study); - the expected distribution of this primary outcome (Gaussian or not), and – if Gaussian – the expected SD at least in the control group; - the expected effect size on this primary outcome (e.g., a between-group difference, for a numerical outcome); - when you have two sub-studies, two calculations must be done separately (unless you can show that the primary outcome behaves similarly with the two measurements). Finally, more minor comments about the presentation: - Introduction, first part: update the references, see above. - Discussion: there is no need to repeat the introduction; as there are no results, just focus on the internal validity (limitation and biases); we had discussed the issue of hypotension in our paper, ref. [5]. Reference List 1. Nissen P. Neurocrit Care 2010; 12:17-23. 2. Foss VT. Front Physiol 2014; 5:81. 3. Meng L. Br J Anaesth 2011; 107:209-217. 4. Pennekamp CW. Br J Anaesth 2012; 109:831-833. 5. Aliane J. Clin Exp Pharmacol Physiol 2017; 44:739-748.

REVIEWER	Paul Soeding Royal Melbourne Hospital, University of Melbourne Melbourne, Victoria, Australia No Competing Interest
REVIEW RETURNED	06-Aug-2017

GENERAL COMMENTS	REVIEW : Effect of ephedrine (E) and phenylephrine (PE) on brain oxygenation and microcirculation in anesthetized patients with cerebral tumors: study protocol for a randomized controlled trial. This prospective randomised trial questions the effect E and PE have on microcirculatory blood flow and oxygenation within the brain. This is particularly relevant in their cohort of 48 patients each with an intracranial tumour. The authors assert MAP has poor correlation with microcirculatory flow, and “paradoxically, lead to reduced capillary perfusion and oxygenation..”(ref 2-4). This question has been raised before, as with the use of vasopressin in traumatic brain injury (Menon et al).

	The study proposes to compare E and PE using MRI and PET. MRI and PET are not sequential in individuals, but performed in separate groups randomised to either E or PE. Preliminary comments There is interest in the difference effects vasopressors have on CPP and microcirculatory flow, particularly since a number of studies indicate frontal lobe cerebral desaturation to be dependent on vasopressor type. Variation in clinical practice also determines whether E, PE or indeed noradrenaline or other medication is used to augment CPP. Secondly receptor heterogeneity and activation account for many of these differences, and it is well known that combined alpha-1 and beta-1 effects of ephedrine can influence organ function differently to the predominate alpha-agonism of phenylephrine. This is evident with cardiac output where both can increase MAP but CO may decrease with PE (LV impedance) and increase with E (Beta-1 effect). Changes in CO itself may potentially affect CBF though MAP may be equal with both vasopressors. The dynamic integration between cerebral and systemic circulations is a fundamental consideration when comparing vasopressor effects on cerebral perfusion. As implied by the authors, a limitation of current practice is our inability to monitor CBF during surgery, though indirect monitoring of cerebral oxygen saturation is applicable in some cases of neuroanaesthesia. Maintenance of systemic MAP remains a central component of clinical practice. However infusion of E may exhibit tachyphylaxis which begs the question as to how will these findings be translated into clinical practice. The authors conclude that findings will improve understanding of commonly used vasopressors. It could be argued that noradrenaline with both alpha and beta-1 properties may have been also a valid choice to study, though it is reported to induce cerebral desaturation. An interesting aspect is how frontal ScO2 may correlate with MRI/PET findings. Specific points 1. There is no discussion concerning adrenoreceptor distribution within the cerebral vasculature, a basic question for the observation that some vasopressors cause cerebral desaturation. Admittedly this is for discussion. 2. Anaesthetic technique needs to be standardized to ensure all patients have similar Cmr02. Firstly why suxamethonium? Is non-depolarising relaxation used thereafter? If not is increased remifentanil administration sufficient to ensure immobility? Whilst ET CO2 is adjusted there is no mention of temperature, or means to ensure patient warmth. 3. There is no mention of an intervention protocol, particularly when vasopressor infusion induces hypertension or reflex bradycardia. How will patients be protected and haemodynamically stabilized to ensure comparable CBF? 4. Vasopressors have different equipotency and individual

	responses vary, indicating a clinical endpoint is necessary. Definition of post-induction baseline with 20% rise post infusion is valid. 5. Head position and neck compression. Posture and cerebral venous congestion can influence ScO2, as well as other measurements such as transit time. There are constraints with MRI cradles etc but this should be recognized when performing study. 6. The sample number appears slightly low, is it appropriately based on expected effect size and known dispersion of effect from previous studies. Sample size estimation is important in such a study, and understandably is dependant on both patient presentation and MRI/PET resources. Have the authors a G-power calculation or equivalent to verify their sample number. This would avoid any concerns with underpowering. Secondly what is meant by "standard parametric testing"? Is student t test appropriate? It is a well-designed and relevant study. Combined MRI and PET is complimentary, and can provide powerful information relating to cerebral supply/demand at the microcirculatory level. However endpoints are non-invasive and derived, and are also subject to limitation, which requires valid interpretation. Notwithstanding such studies (particularly fMRI studies) have provided valuable correlation in investigation of Pain and mechanisms of Cerebral oximetry (eg Phan Adv Exp Med Biol. 2016;923:195-201.)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Christian Dualé
Institution and Country: CPC-CIC, CHU de Clermont-Ferrand, France
Competing Interests: None declared

The randomization is conducted with rather big blocks (of 12), while there are two studies of 12 vs. 12: what is done is done, I just hope there will not be bad surprises at the end…

We acknowledge not having clarified the exact block randomization process. In part 1 and 2 of the study, block randomization is performed in blocks of 10+10+4. We have made changes in the manuscript – please see page 6 section: Randomization and blinding, line 2-5.

Comment: There is few information about the blinding, but I believe that, if the MRI/PET parameters were measured unaware of the treatment given (which is easy to do), this would be a quasi-double-blind study, as the patient can be easily blinded. What was exactly planned?

Response: Patients and investigators are blinded to the randomization. Interpretation of MR imaging and calculation of flow parameters are performed by a blinded investigator. After final inclusion, an independent assistant will unblind the two groups and subsequently label the groups 0 and 1. Statistical analysis will be performed and, eventually, final unblinding will take place. We have made changes in the manuscript – please see page 6 section: Randomization and blinding, line 10-13.

Comment: My first big concern is about the clinical relevance. The authors state that vasopressors "are commonly used during brain tumor surgery to maintain sufficient cerebral perfusion pressure (CPP) in order to ensure adequate cerebral oxygenation", but the reference given to support this relates only to traumatic brain injury (Bratton SL et al., ref n°1). This must justify the protocol, in which

patients had an intravenous infusion of either ephedrine (2mg/ml) or phenylephrine (0.1mg/ml) “until main arterial blood pressure (MABP) increases to above 60 mmHg, or by 20% relative to the baseline”. I can admit that a good cerebral perfusion is always preferable in surgeries at risk of damaging brain, but does this justify a systematic infusion of vasopressors, furthermore to induce a mild hypertension, rather than a normotension? At this point (as the study is already initiated), the authors have these options:

- either to provide published recommendations to justify a mild hypertension in such surgeries;
- or to admit that the vasopressors were not administered for what they are currently indicated (intraoperative hypotension), so the pharmacological conditions are not exactly these of the clinical practice, and the results should be interpreted with caution;
- a third possibility would be if the so called “baseline” (which is actually “the first MABP measured at the time of the initial MRI or PET sequence”) was actually an hypotensive condition: in this case, the conditions of administration would be correct, but with ethical concerns (the treatment should have been given earlier…).

Response: No specific hemodynamic recommendations exist concerning anesthesia management of patients undergoing craniotomy for cerebral tumors. Consequently, we refer to a study with other space occupying cerebral pathology where similar hemodynamic considerations may apply (Bratton et al.). Furthermore, it is common practice during brain tumor surgery to secure cerebral perfusion and oxygenation with elevated or supranormal MABP values. Accordingly, we provide further argumentation for the use of vasopressors in patients undergoing craniotomy and further added supplementary references with MABP values which correspond to the values in our study*. We have made changes in the manuscript – please see page 4 section: Introduction, line 1 to 15.

* (Rasmussen M; Deepak et al.; Dengsøe et al.; Palazon et al.; Sookplung P et al.; Meng L; Foss VT et al.; Pennekamp CW; Aliane J)

Comment: My second big concern is about the sample size calculation. The current manuscript states that the primary endpoints are “between-groups absolute and relative differences in CBF, CBV, MTT, CTH and calculated and measured CMRO2 and OEF respectively”. This is not correct (as there would be 14 outcomes), and not in accordance to the declaration on ClinicalTrials.gov, in which only the CTH (I suppose, its absolute value for each sub-study) is declared as the primary outcome.

Response: We recognize that it is only possible to have one primary endpoint. We have made changes in the manuscript – please see page 9 section: Endpoints, line 2-5.

Comment: So, let us consider that CTH is the primary outcome, and read now the sample size calculation: the type-I and type-II errors are good, but was the hypothesis bilateral?

Response: The hypothesis is bilateral (two-sided), as mentioned by the reviewer” preferable in a pilot study”

Comment: the expected effect size is a “10% increase in CTH giving infusion phenylephrine compared to ephedrine”: must we understand that there will be a 10%-increase of CTH under phenylephrine, vs. a 0%-increase under ephedrine, or a difference of 10% between groups, but 10% of what?

Response: We expect a difference of 10% in the change of CTH value, when comparing the effects of phenylephrine and ephedrine before and after infusion, that is:

%

Comment: to what refers the “difference in mean of 0.3216 ± 0.2”, I do not see anything like that in the two given references (Rasmussen M et al., 2010, n°26; Rasmussen M et al., 2004, n°27).
I must remind that the following information must clearly given (in addition to the type-I and type-II errors):
the predefined primary outcome (e.g. the CTH, or the effect of the drug on the CTH, expressed as a percentage/rate of the pre-treatment value);

Sample size estimation was calculated with a power analysis in STATA14 on a basis of earlier pilot studies with calculations of CTH. A 10% difference was found as a significant clinical change. Also changes in studies on cerebral oxygenation measured with NIRS, a difference of 10% was found significant. No data exist on vasopressor therapy with CTH as the primary endpoint. Consequently, based on our current experience with CTH, the expected 10% difference in CTH was translated into an estimated pre-vasopressor MRI-CTH value of 3,216 seconds and a 10% difference giving a mean difference of 0.3216 seconds.(%). We have made changes in the manuscript – please see page 10 section: Statistics, line 1-17.

- the hypothesis (unilateral or bilateral; bilateral is preferable in a pilot study);
- the expected distribution of this primary outcome (Gaussian or not), and – if Gaussian – the expected SD at least in the control group;
- the expected effect size on this primary outcome (e.g., a between-group difference, for a numerical outcome);

Response: As mentioned earlier, the hypothesis is two-sided. As our power calculation shows we expect the data to be of normal distribution well aware the number of patients is below 30. Specific tests include paired t-test or Wilcoxon signed rank test for paired data analysis and unpaired t-test or Mann-Whitney U test for testing of between group differences. We recognize that it is difficult to be precise about the SD, but we used the best estimate of 0.2 in conjunction with our statistician.
Effect size between groups 10% of 3.216 seconds, that is 0.3216 seconds. We have made changes in the manuscript – please see page 10 section: Statistics, line 1-17.

Comment: when you have two sub-studies, two calculations must be done separately (unless you can show that the primary outcome behaves similarly with the two measurements).

Response: We expect the same change in CTH in the two sub-studies, as nothing besides imaging modality has changed between the two studies.

Comment: Finally, more minor comments about the presentation:
Introduction, first part: update the references, see above.
Discussion: there is no need to repeat the introduction; as there are no results, just focus on the internal validity (limitation and biases); we had discussed the issue of hypotension in our paper, ref. [5].

Response: We have made changes in the manuscript – please see page 11 section: Discussion, line 4-6.

Reference List
1. Nissen P. Neurocrit Care 2010; 12:17-23.
2. Foss VT. Front Physiol 2014; 5:81.
3. Meng L. Br J Anaesth 2011; 107:209-217.
4. Pennekamp CW. Br J Anaesth 2012; 109:831-833.
5. Aliane J. Clin Exp Pharmacol Physiol 2017; 44:739-748.

We have made changes in the manuscript – please see page 15-17 section: References

Reviewer: 2
Reviewer Name: Paul Soeding
Institution and Country: Royal Melbourne Hospital, University of Melbourne Melbourne, Victoria, Australia
Competing Interests: None

Specific points
1. There is no discussion concerning adrenoreceptor distribution within the cerebral vasculature, a basic question for the observation that some vasopressors cause cerebral desaturation. Admittedly this is for discussion.

Response: We agree with the reviewer. However, we do not find that the discussion concerning distribution of adrenoreceptors is relevant in this protocol paper. In the final report, it is relevant to include this important aspect of discussion. Accordingly, we have not made any changes in the manuscript.

2. Anesthetic technique needs to be standardized to ensure all patients have similar Cmr02. Firstly, why suxamethonium? Is non-depolarising relaxation used thereafter? If not is increased remifentanil administration sufficient to ensure immobility? Whilst ET CO2 is adjusted there is no mention of temperature, or means to ensure patient warmth.

Response: A low dose of Suxamethonium is administered in order to facilitate intubation. This is done in order to reduce the risk of severe hypotension after high induction doses of propofol and remifentanil. Non-depolarising relaxation is not used. It is important to emphasize that BIS-monitoring is used during induction to ensure adequate depth of anesthesia. Propofol and remifentanil is administered to ensure immobility. Temperature is monitored as soon as the patient arrives in the OR – equipment for temperature measurement is not MR-compatible. The patient is kept warm in the scanner with sheets and blankets, furthermore the MRI increases temperature in the patient's body during the scan. We have made changes in the manuscript – please see page 6-7 section: Anesthesia and monitoring, line 1-6 and 9-13.

3. There is no mention of an intervention protocol, particularly when vasopressor infusion induces hypertension or reflex bradycardia. How will patients be protected and hemodynamically stabilized to ensure comparable CBF?

Response: If unacceptable hypertension occurs, the infusion rate of study drug is reduced. In addition, if reflex bradycardia occurs we consider reducing study drug infusion rate or administration of atropine. We have made changes in the manuscript – please see page 7 section: Intervention and study drugs, line 6-8.

4. Vasopressors have different equipotency and individual responses vary, indicating a clinical endpoint is necessary. Definition of post-induction baseline with 20% rise post infusion is valid.

Response: It is important for us that the dosage of vasopressors examined in this study reflects the dosage regime and endpoints used in daily practice. Otherwise, this study would not add data to potentially ease the decision of the anesthesiologists in their choice of vasopressor. We had some

considerations concerning this aspect and we are glad the reviewer acknowledges our choice of endpoint. We have not made any changes in the manuscript.

5. Head position and neck compression. Posture and cerebral venous congestion can influence ScO2, as well as other measurements such as transit time. There are constraints with MRI cradles etc but this should be recognized when performing study.

Response: The reviewer emphasizes an important issue. We are aware that head position is kept neutral without any neck rotation. The patient is supine and neck rotation and compression cannot occur in our MRI head cradles. We have made changes in the manuscript – please see page 6-7 section: Anesthesia and monitoring, line 1-6 and 9-13.

6. The sample number appears slightly low, is it appropriately based on expected effect size and known dispersion of effect from previous studies. Sample size estimation is important in such a study, and understandably is dependent on both patient presentation and MRI/PET resources. Have the authors a G-power calculation or equivalent to verify their sample number. This would avoid any concerns with under powering. Secondly what is meant by “standard parametric testing”? Is student t test appropriate?

Response: Sample size estimation was calculated with a power analysis in STATA14 on a basis of earlier pilot studies with calculations of CTH. A 10% difference was found as a significant clinical change. Also changes in studies on cerebral oxygenation measured with NIRS, a difference of 10% was found significant. No data exist on vasopressor therapy with CTH as the primary endpoint. Consequently, based on our current experience with CTH, the expected 10% difference in CTH was translated into an estimated pre-vasopressor MRI-CTH value of 3.216 seconds and a 10% difference giving a mean difference of 0.3216 seconds. Furthermore, the reviewer’s observation on dependence of patient presentation and scanner availability are most correct.

Data will be analyzed using conventional appropriate test statistics depending on the distribution of the individual outcome parameters. Specific tests include paired t-test or Wilcoxon signed rank test for paired data analysis and unpaired t-test or Mann-Whitney U test for testing of between group differences. We have made changes in the manuscript – please see page 10 section: Statistics, line 1-17.

Furthermore, we agree with the reviewer that it would be interesting to study norepinephrine in the same setting. This was not the intention in our study but would surely be relevant for future studies.

Further changes have been made:

Word count page 1

To clarify strengths and limitations: page 3 section: Strengths and limitations, line 2, 4, 9 and 11

To clarify on SPIRIT checklist item 21a: page 12 section: Ethics approval and consent to participate, line 1-2

To clarify on SPIRIT checklist item 22: page 12 section: Ethics approval and consent to participate, line 5-14

To clarify on SPIRIT checklist item 26a: page 5 section: Patients, line 2

To clarify on SPIRIT checklist item 31a: page 2 section: Ethics and dissemination line 2-3 and page 10-11 section: Study management, line 6-8

To clarify on fig. 2: page 18 section: Figure legends, line 3-

VERSION 2 – REVIEW

REVIEWER	Christian Dualé CPC-CIC CHU Clermont-Ferrand France
REVIEW RETURNED	11-Sep-2017

GENERAL COMMENTS	The points for which concerns had been raised have been addressed properly. Here are just remaining minor comments: - about the referenced comparisons of the two vasopressors during carotid endarterectomy : note that the study of Pennekamp CW et al. (Br J Anaesth 2012; 109:831) was only observational, while a double-blind RCT has been published since then Aliane J. Clin Exp Pharmacol Physiol 2017; 44:739). - In the sample size calculation the reference n° 33 of Brassard et al. does not really relate to an effect size between the two vasopressors, as only phenylephrine was tested in this study.

REVIEWER	Paul Soeding Royal Melbourne Hospital, Australia and University of Melbourne, Australia
REVIEW RETURNED	27-Sep-2017

GENERAL COMMENTS	This study utilises powerful imaging technology to monitor regional CBF using parameters such as perfusion mapping. The design flows well with patient management. A key question is whether these tools have sufficient resolution to discern such changes in microcirculatory flow within normal parenchyma and around tumours. Cerebral oximetry remains indirect in assessing rCBF, in contrast the strength of this study is direct observation of rCBF. Should ephedrine be demonstrated to be favourable, then the translation into neuroanaesthetic practice remains interesting, in view of possible tachyphylaxis for prolonged procedures. The team expertise is strong.

VERSION 2 – AUTHOR RESPONSE

Thank you very much for the recommendation. The article Aliane J. Clin Exp Pharmacol Physiol 2017; 44:739 has been added to the references as number 18 and is refered in the introduction section.

Further the reference n° 33 of Brassard et al. has been deleted in the statistics section and replaced with the reference Foss VT, Christensen R, Rokamp KZ et al.

VERSION 3 – REVIEW

REVIEWER	Christian Dualé CPC-CIC, CHU Clermont-Ferrand, France
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	All the critical points have been addressed.