PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Feasibility of Improving Cerebral Autoregulation in Acute Intracerebral Haemorrhage (BREATHE-ICH) Study: A Protocol for an Experimental Interventional Study
AUTHORS	Minhas, Jatinder; Panerai, Ronney; Robinson, Tom

VERSION 1 – REVIEW

REVIEWER	Patricia Fogarty Mack Weill Cornell Medicine
REVIEW RETURNED	06-Dec-2017

GENERAL COMMENTS	Page 4 line 15 needs grammatical editing with a comma after "studies" instead of a period. Page 6 line 20 Change to "against both potential vasoconstriction leading to hypocapnea induced brain ischaemia as well as cerebral hperemia due to subsequent..... Page 6 Line 30 CHange to "different from" Page 6 line 54-55 Page 7 line 3: needs clarification.. do you mean "possibly being of greater clinical benefit than methods..... I am concerned about the accuracy of ETCO2 measurements vial salter nasal cannulae, especially in voluntary hyperventilation. I guess you are already proceeding, but do you have access to any trasncutaneos CO2 measurement devices. In any event you ought to put a potential lack of accuracy in ETCO2 measurements via nasal cannula in your discussion of limitations. Q4. Please describe the hyperventilation technique in more detail? vital capacity breaths?will you have a practice period? Q.6. Please be more specific with the outcome goals ie what percentage of patients were able to comply. Was there a preservation of autoregulation?

REVIEWER	Craig Anderson The George Institute Australia
REVIEW RETURNED	29-Dec-2017

GENERAL COMMENTS	This manuscript reports the protocol for a mechanistic/feasibility study of the use of simple induced hypocapnia in patients with acute intracerebral haemorrhage (ICH), the most serious form of stroke where elevation of intracranial pressure from haematoma mass

	effect and perihematomal oedema have important influences on outcome. The trial is novel and has substantial background rational support from use of the approach in other clinical populations and prior work from this group in a health population. The main concerns relate to the following that have not been adequately addressed in the protocol 1) while I recognise that this is a feasibility and proof-of-concept study over efficacy/safety on cerebral blood flow determined by transcranial doppler, if this was to translate into a therapeutic treatment then it is likely to have the most effect in patients who present early. Thus, why has a 48 hour time window form the onset of symptoms been chosen - while this allows for clinical stability, it also means that those patients who present early and then deteriorate have been excluded. Moreover, those with mild stable haematomas who are likely to adhere to the treatment have the less to gain from it. 2) While this is a simple bedside test, it is to be undertaken in a cardiovascular laboratory within the hospital and require patient transfer and monitoring. Why have the investigators not chosen to bring the laboratory to the patient - this will likely increase recruitment, patient and clinician acceptability, lower transfer risks and generalisability. 3) Mention could be made in the background about the implications of cerebral ischaemic lesions noted on MRI in patients with acute ICH raising the possibility of harms associated with BP lowering which may be more relevant than issues of perihaemoatomal ischaemia. 4) The sample size of 45 patients has been derived from the investigator's work in health subjects, but this is likely to increase in ICH patients due to greater clinical variability, confounding factors, and missing data. The investigators may wish to consider their sample size and also recruitment feasibility based on number of ICH cases through a single hospital. 5) although a committee is monitoring safety in the study, this is organised internally and open to conflict of interest over science and ethics. It would be better to have an associated independent data monitoring committee reviewing the accumulated data at regular intervals and reporting to the steering committee/PI.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

Page 4 line 15 needs grammatical editing with a comma after "studies" instead of a period.
REPLY – Thank you for highlighting this. The authors have changed it accordingly.

Page 6 line 20 Change to "against both potential vasoconstriction leading to hypocapnea induced brain ischaemia as well as cerebral hyperemia due to subsequent.....
REPLY – Thank you for this suggestion. The authors have changed it accordingly.

Page 6 Line 30 CHange to "different from"
REPLY – Thank you for highlighting this. The authors have changed it accordingly.

Page 6 line 54-55 Page 7 line 3: needs clarification.. do you mean "possibly being of greater clinical benefit than methods.....

REPLY – Thank you for highlighting this. The authors have changed this sentence as you kindly advise to improve the clarity of the statement.

I am concerned about the accuracy of ETCO2 measurements vial salter nasal cannulae, especially in voluntary hyperventilation. I guess you are already proceeding, but do you have access to any trasncutaneos CO2 measurement devices. In any event you ought to put a potential lack of accuracy in ETCO2 measurements via nasal cannula in your discussion of limitations.

REPLY – This is a pertinent comment. The authors did consider this, however, prior literature suggests that transcutaneous measures can be inaccurate and have a very slow response time (Janaillac et al. 2016 Crit Care Res Pract), but more importantly the benefits over nasal PaCO2 methods are confined largely to obese patients with a functional residual capacity that is reduced with resultant ventilation-perfusion inequalities (Griffin et al. 2003 BJA). Nevertheless, as the authors have conducted prior methodological work demonstrating a slight underestimation of PaCO2 using nasal cannulae vs face mask, we have included this in the limitations section as suggested.

Q4. Please describe the hyperventilation technique in more detail? vital capacity breaths?will you have a practice period?
REPLY – Thank you for highlighting this. The authors have changed the content of the 'Intervention' section to provide more clarity.

Q.6. Please be more specific with the outcome goals ie what percentage of patients were able to comply. Was there a preservation of autoregulation?
REPLY – Thank you for highlighting this. The authors have changed the content of the 'Interpretation' section to provide more clarity.

Reviewer #2:
This manuscript reports the protocol for a mechanistic/feasibility study of the use of simple induced hypocapnia in patients with acute intracerebral haemorrhage (ICH), the most serious form of stroke where elevation of intracranial pressure from haematoma mass effect and perihematomal oedema have important influences on outcome. The trial is novel and has substantial background rational support from use of the approach in other clinical populations and prior work from this group in a health population.
Thank you Reviewer 2 for your kind summary of our work and positive comments regarding the content of the manuscript.

The main concerns relate to the following that have not been adequately addressed in the protocol
1) while I recognise that this is a feasibility and proof-of-concept study over efficacy/safety on cerebral blood flow determined by transcranial doppler, if this was to translate into a therapeutic treatment then it is likely to have the most effect in patients who present early. Thus, why has a 48 hour time window form the onset of symptoms been chosen - while this allows for clinical stability, it also means that those patients who present early and then deteriorate have been excluded. Moreover, those with mild stable haematomas who are likely to adhere to the treatment have the less to gain from it.
REPLY – This is a pertinent comment. The authors did consider a narrower time window, however, the window itself does not detract from the specific aim of recruiting all individuals as soon as possible after ICH onset. However, prior work by Nakagawa et al. (2011, BMC Neurology), demonstrated dCA was most impaired in period <72hrs after onset. The authors therefore considered 48 hours an acceptable window given the proof-of-concept nature of the study, but agree that in a future definitive intervention trial it would be important to recruit an ICH population as soon as possible after onset.

2) While this is a simple bedside test, it is to be undertaken in a cardiovascular laboratory within the hospital and require patient transfer and monitoring. Why have the investigators not chosen to bring

the laboratory to the patient - this will likely increase recruitment, patient and clinician acceptability, lower transfer risks and generalisability.
REPLY – We are grateful to Reviewer 2 highlighting this lack of clarity. Figure 1 demonstrates the "mobile laboratory" that we take to the patient's bedside on the hyperacute stroke unit when they are unable to transfer to our nearby laboratory for study measurement. In order to improve clarity of this, the authors have added a comment to the 'Data collection and integration' section to this effect.

3) Mention could be made in the background about the implications of cerebral ischaemic lesions noted on MRI in patients with acute ICH raising the possibility of harms associated with BP lowering which may be more relevant than issues of perihaemoatomal ischaemia.
REPLY – Thank you for highlighting this. The authors have changed the content of the 'Background' section to highlight this important point.

4) The sample size of 45 patients has been derived from the investigator's work in health subjects, but this is likely to increase in ICH patients due to greater clinical variability, confounding factors, and missing data. The investigators may wish to consider their sample size and also recruitment feasibility based on number of ICH cases through a single hospital.
REPLY – This is a pertinent comment. The authors have considered this and acknowledge that the sample size of n=45 relates to the likelihood of a lack of temporal windows, as well as the important points the reviewer raises. Therefore, the authors hope to recruit 45 individuals with acceptable and analysable data ideally as a minimum. However, as this is a feasibility study, acknowledgement for these limitations within the study population is also a crucial study metric.

5) Although a committee is monitoring safety in the study, this is organised internally and open to conflict of interest over science and ethics. It would be better to have an associated independent data monitoring committee reviewing the accumulated data at regular intervals and reporting to the steering committee/PI.
REPLY – This is a pertinent comment. For a definitive trial, the investigators would clearly seek to appoint an independent DMC. However, in the context of a feasibility study, the authors agree that we should seek an independent clinician from within our institution to ensure that there is no perceived conflict of interest over science and ethics.

VERSION 2 – REVIEW

REVIEWER	Patricia Mack MD Weill Cornell Medicine
REVIEW RETURNED	14-Feb-2018

GENERAL COMMENTS	The modifications made in response to the comments of reviewer 1 enhance the description of the protocol.

REVIEWER	Craig Anderson The George Institute, Sydney, Australia
REVIEW RETURNED	17-Feb-2018

GENERAL COMMENTS	The authors have adequately addressed reviewer comments