PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Aneurysmal subarachnoid hemorrhage- cerebral vasospasm and prophylactic Ibuprofen: A randomised controlled pilot trial protocol
AUTHORS	Dayyani, Mojtaba; Mousavi Mohammadi, Ermia; Ashoorion, Vahid; Sadeghirad, Behnam; Javedani Yekta, Mohammadreza; Grotta, James; Gonzalez, Nestor; Zabihyan, Samira

VERSION 1 – REVIEW

REVIEWER	Thudium, Marcus Universitatsklinikum Bonn
REVIEW RETURNED	15-Dec-2021

GENERAL COMMENTS	The authors present a study protocol concerning an interesting approach to vasospasm therapy. The protocol is well written and straightforward. However, a few things remain unclear: The authors plan to investigate feasibility as in adherence to the protocol. Assuming this is a single-center study, how about the following trial? Do you expect low adherence to the protocol? Please explain the necessity of a feasibility study. While safety considerations are thoroughly discussed, it remains unclear at what point the study medication can be considered safe or if the number of 30 patients is sufficient for a safety statement. Please comment. If the mentioned 30 patients are to be included in the definitive study, data about the effect of the medication will have to be gathered as it is mentioned in “objectives for the definitive trial”. How do the authors define “delayed cerebral ischemia”? The evolution of vasospasm is documented exclusively by TCD? How, if at all is the neurological exam objectified?

REVIEWER	Macdonald, R Loch Community Regional Medical Center, Neurosurgery
REVIEW RETURNED	06-Jan-2022

GENERAL COMMENTS	This is a protocol for a study of ibuprofen administration in patients with subarachnoid hemorrhage (SAH). Abstract intro – is CVS the main cause of M and M after SAH? I think not, it is more like the effects of the initial hemorrhage. And inflammation has been thought to be involved for decades. It will be involved almost by definition since inflammation is response of body tissue to injury and SAH is an injury.

	Admission within 12 hours of the SAH is very rapid and is going to limit recruitment, there must be some important rationale for this. 12 hours in rabbits may or may not be equal to 12 hours in humans. None of the prior NSAID/ASA studies are sufficient in size to draw any conclusions about drug effect and even safety. It is recommended to consider using the terminology for CVS and delayed ischemic neurologic deficit as defined by Vergouwen, Stroke 2010. DCI is a clinical diagnosis. TCD is unreliable. Aneurysm SAH is confirmed by CT and a vascular imaging study not CT or CTA… etc. Primary objective – isn't it safety, tolerability and feasibility not mortality – mortality is very low in WFNS 1-3 patients and is not going to be different between groups here. Followup of 29/30 also is high, is that statistically necessary ie about 3% lost to followup in the study? I thought up to 10% might be ok. The protocol doesn't say what system is used for adverse events – usually there is use of the Medra coding or I think there is a cancer care system for definition and classification that is used commonly. And all of the usual ibuprofen side effects are going to be hard to detect in SAH patients, they all have headaches and nausea and such. I've never heard of MI and hypertension being problems with ibuprofen. Of course you will collect all of these. In the US at least there is requirement to report serious AE I think within 24 hours, although this is an approved drug so not sure anything needs to be reported, just recorded for study purposes.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Marcus Thudium, Universitatsklinikum Bonn
Comments to the Author:
The authors present a study protocol concerning an interesting approach to vasospasm therapy. The protocol is well written and straightforward.
However, a few things remain unclear:

- The authors plan to investigate feasibility as in adherence to the protocol. Assuming this is a single-center study, how about the following trial? Do you expect low adherence to the protocol? Please explain the necessity of a feasibility study.

Author's response: Thanks for your interest. As recruitment of eligible participants in a narrow time window (12-hour) after the occurrence of aSAH is a challenging inclusion criteria, it may slow down the advancement of the trial, specially at larger scales. Conduction of a large phase III trial poses fundamental challenges for methodological design as well as complexities of execution. Thus, a prerequisite pilot trial is required to justify if the preliminary plan can be implemented in a larger definitive trial. Based on the effect estimates coming out of this pilot study, we will calculate a proper sample size for the definitive trial and will assess and troubleshoot the potential executive barriers for the next step.

- While safety considerations are thoroughly discussed, it remains unclear at what point the study medication can be considered safe or if the number of 30 patients is sufficient for a safety statement.

Please comment.

Author's response: Thanks for pointing out this issue. Pilot trials are typically not powered to detect meaningful differences in clinically important endpoints, including harm. There is also very limited evidence/guidance on stopping rule for harm in superiority trials (particularly in definitive designs) which is because if the treatment of interest is associated with important harm(s) then there is the question of clinical equipoise1 2. On the other hand, ibuprofen with doses intended for this study is generally proven to be safe. Despite the above, we added the following statement to the manuscript: "Administration of the study drug ceases if any serious adverse events happen or adverse effects prevent the tolerability of the Ibuprofen (Supplemental digital content, parts 5, 6) or the patient wishes to withdraw the consent before the study ends". (lines 319-322-marked manuscript)
Additionally, based on the recommendation of extension of the CONSORT Statement on Better Reporting of Harms in Randomized Trials3, we will collect and appropriately report all good and bad events and outcomes so that they may be compared across treatment groups (if we have enough power to detect statistically important difference between trial arms for potential harm). Also, according to the same statement, the topic of "balance of benefits and harm" will be discussed in the final publication of the pilot trial. In addition, for assessing the severity of adverse events (including clinical and laboratory abnormalities) and grading of them among the participants we will use the guideline by National Institute of Allergy and Infectious Diseases, entitled: "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.4" Explanations mentioned above are added to the "safety considerations" section of the manuscript (lines 323-338- marked manuscript).

- If the mentioned 30 patients are to be included in the definitive study, data about the effect of the medication will have to be gathered as it is mentioned in "objectives for the definitive trial". How do the authors define "delayed cerebral ischemia"? The evolution of vasospasm is documented exclusively by TCD? How, if at all is the neurological exam objectified?

Author's response: Detailed definition of DCI can be found in Supplemental digital content 3 (SDC part 3, Page 4). The following statement in blue is added to the (SDC part 3, Page 4): Acceptable definitions for DCI were the development of new, focal neurological deficits, and/or a decreased level of consciousness of at least two points on the Glasgow Coma Scale after other possible causes of deterioration have been excluded or a new infarct revealed by follow-up brain computed tomography5 6, or increases at least two scores of the National Institutes of Health Stroke Scale (NIHSS) 7; in this condition, vasospasm will be confirmed by TCD. Details of the flow velocity measurements of the middle cerebral artery (MCA) and the basilar artery is discussed in SDC Part 3 (Page 4).

Reviewer: 2
Dr. R Loch Macdonald, Community Regional Medical Center
Comments to the Author:
bmjopen-2021-058895_Proof_hi review

This is a protocol for a study of ibuprofen administration in patients with subarachnoid hemorrhage (SAH).

- Abstract intro – is CVS the main cause of M and M after SAH? I think not, it is more like the effects of the initial hemorrhage. And inflammation has been thought to be involved for decades. It will be involved almost by definition since inflammation is response of body tissue to injury and SAH is an injury.

Author's response: Thanks for your comment; we agree with the concept in general and on page 5,

lines 128-132 (marked manuscript) we mentioned that “cerebral vasospasm following aSAH (not solely cerebral vasospasm) is the leading cause of mortality and morbidity 8-10. The exact mechanisms of the complex inflammatory cascade leading to cerebral vasospasm is not well understood, and usual treatments have no sufficient therapeutic effects 11-14. However, several studies support the hypothesis that local and systemic inflammatory responses may participate in the process of cerebral vasospasm and its consequent poor outcomes.”

- Admission within 12 hours of the SAH is very rapid and is going to limit recruitment, there must be some important rationale for this. 12 hours in rabbits may or may not be equal to 12 hours in humans. None of the prior NSAID/ASA studies are sufficient in size to draw any conclusions about drug effect and even safety.

Author’s response: Thanks for your comment. As we have mentioned in the section “Strengths and limitations of this study”, recruitment of eligible participants in a narrow time window (12-hour) after the occurrence of aSAH is a challenging inclusion criteria that may slow down the advancement of the trial. However, this short window time for prophylactic treatment is one of the cornerstones of our novel hypothesis and does not solely rely on 12-hour interval in rabbits but mainly relies on the process of the acute phase of inflammation that starts 3-4 hours after the SAH15, and the specific pharmacodynamics of the ibuprofen as a fast acting NSAID which could potentially prevent from binding of macrophages and neutrophils to the endothelial cells and entering the subarachnoid space; hence, reducing the intensity of acute phase inflammation. This inhibitory action, will decrease the number of trapped leukocytes dying and degranulating in the subarachnoid space in the next 2 to 4 days15, and subsequently may reduce or prevent chronic vasospasm in the upcoming days of admission.
Also, it is to note that pilot trials are typically not powered to detect meaningful differences in clinically important endpoints and to draw conclusion on the effectiveness or safety of treatments1 2.

- It is recommended to consider using the terminology for CVS and delayed ischemic neurologic deficit as defined by Vergouwen, Stroke 2010. DCI is a clinical diagnosis. TCD is unreliable.
Author’s response: Thanks for your suggestion. We used the term DCI based on the terminology and the definitions by Vergouwen et al5 and also according to the National Institute of Neurological Disorders and Stroke (NINDS) common data elements for SAH.

- Aneurysm SAH is confirmed by CT and a vascular imaging study not CT or CTA… etc.

Author’s response: Thanks for pointing out this issue. We modified the sentence for clarification we added the conjunctions “and” / “or” as below:
“aneurysmal subarachnoid hemorrhage confirmed by a brain CT scan, and CT angiography, or magnetic resonance angiography, or digital subtraction angiography.”

- Primary objective – isn’t it safety, tolerability and feasibility not mortality – mortality is very low in WFNS 1-3 patients and is not going to be different between groups here. Followup of 29/30 also is high, is that statistically necessary ie about 3% lost to followup in the study? I thought up to 10% might be ok.

Author’s response: Pilot trials are typically not powered to detect meaningful differences in clinically important endpoints, including harm. There is also very limited evidence/guidance on stopping rule for harm in superiority trials (particularly in definitive designs) which is because if the treatment of interest is associated with important harm(s) then there is the question of clinical equipoise1 2.
We understand your concern regarding definition of feasibility. We have discussed three possible conditions for this issue in the sample size section under the heading Methods (lines 263-268-marked manuscript). Your concern is addressed as below: “If 29/30 participants achieve successful

follow-up, the lower boundary of the 95% confidence interval will be above 85%, and we will consider the trial feasible. If less than 22/30 achieve complete follow-up, the upper boundary of the confidence interval will be below 85%, and we will consider the trial unfeasible. Therefore, if between 22 and 29 out of 30 patients complete a 3-month follow-up, the feasibility of the trial will remain uncertain; however, we will consider this satisfactory."

- The protocol doesn't say what system is used for adverse events – usually there is use of the Medra coding or I think there is a cancer care system for definition and classification that is used commonly. And all of the usual ibuprofen side effects are going to be hard to detect in SAH patients, they all have headaches and nausea and such. I've never heard of MI and hypertension being problems with ibuprofen. Of course you will collect all of these. In the US at least there is requirement to report serious AE I think within 24 hours, although this is an approved drug so not sure anything needs to be reported, just recorded for study purposes.

Author's response: The explanations mentioned below are added to the "safety considerations" section of the manuscript (lines 323-338- marked manuscript).
Based on the recommendation of extension of the CONSORT Statement on Better Reporting of Harms in Randomized Trials3 16, we will collect and appropriately report all good and bad events and outcomes so that they may be compared across treatment groups. Also, according to the same statement, the topic of "balance of benefits and harm" will be placed and discussed in the final publication of the pilot trial. In addition, for assessing the severity of adverse events (including clinical and laboratory abnormalities) and grading of them among the participants we will use the guideline by National Institute of Allergy and Infectious Diseases, entitled: "Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.4"

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