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Prophylactic effects of Ibuprofen on cerebral vasospasm following aneurysmal subarachnoid hemorrhage: Protocol for a randomised placebo-controlled pilot trial

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List of Abbreviations

Abbreviation	Explanation
aSAH	aneurysmal Subarachnoid Hemorrhage
CI	Confidence Interval
COX	Cyclooxygenase
CSF	Cerebrospinal Fluid
CTA	CT Angiography
CVS	Cerebral Vasospasm
DSA	Digital Subtraction Angiography
ICAM-1	Intercellular adhesion molecule-1
ICU	Intensive care unit
TCD	Transcranial Doppler
MRA	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
PSVMCA	Peak Systolic Middle Cerebral Artery Velocity
SIRS	Systemic Inflammatory Response Syndrome
SPIRIT	Standard Protocol Items Recommendation for Interventional Trials
TXA	Thromboxane
VCAM-1	Vascular Cell Adhesion Molecule-1
WFNS	World Federation of Neurological Surgeons

Abstract

Introduction: Cerebral vasospasm (CVS) is the leading cause of mortality and morbidity following aSAH. One of the recently implicated underlying mechanisms of CVS is inflammatory cascades. Specific feasibility objectives include determining the ability to recruit 30 participants over twelve months while at least 75% of them comply with at least 75% of the study protocol and being able to follow 85% of them for three months after discharge.

Methods and analysis: This is a feasibility study for a randomised, controlled trial. Eligible participants are adult patients 18y/o and older with an aSAH confirmed by a brain CT scan, CT angiography, magnetic resonance angiography, or digital subtraction angiography who admitted to the emergency department within 12 hours of the ictus. Eligible subjects will be randomised 1:1 for the administration of either ibuprofen or a placebo, while both groups will concomitantly be treated by the standard of care for two weeks. Care givers, patients, outcome assessors and data analysts will be blinded. This will be the first study to investigate the preventive effects of a short acting NSAID on CVS and the key expected outcome of this pilot study is the feasibility and safety assessment of the administration of Ibuprofen in patients with aSAH. The objectives of the definitive trial would be to assess the effect of Ibuprofen relative to placebo on mortality, CVS, DCI, and level of disability at 3-month follow-up.

Ethics and dissemination: This study is approved by Mashhad University of Medical Sciences ethical committee (IR.MUMS.MEDICAL.REC.1398.225). Results from the study will be submitted for publication regardless of whether or not there are significant findings.

Trial registration: ISRCTN14611625

Keywords: Aneurysmal subarachnoid hemorrhage, Cerebral vasospasm, Delayed cerebral ischemia, Feasibility study, Ibuprofen, Randomised Controlled Trial.

Strengths and limitations of this study

- This is the first pilot trial in which the preventive role of a short-acting oral NSAID (Ibuprofen) is being assessed on cerebral vasospasm in a narrow time window (12-hour) after the occurrence of aneurysmal Subarachnoid Hemorrhage (aSAH).
- The objectives of this pilot study are the feasibility and safety assessment of the administration of Ibuprofen in patients with aSAH.
- The objectives of the definitive trial are to demonstrate the effects of Ibuprofen versus placebo on mortality, cerebral vasospasm, DCI, and level of disability at 3-month follow-up.
- During the pilot trial, we will collect information on all outcomes for the definitive trial.
- To minimize any potential bias, blinding of health care providers (physicians, ICU nurses, residents), patients, outcome assessors, and data analysts to treatment allocation is being undertaken.

INTRODUCTION

Background and Rationale

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 5–10 % of all strokes worldwide, which approximately equals to a total of 600,000 new cases per year [1]. Up to 44% of such cases will die [2], and almost 20% of the survived ones would become disabled and dependent [2]. Cerebral vasospasm following aSAH is the leading cause of mortality and morbidity [3-5]. The exact mechanisms of the complex inflammatory cascade leading to cerebral vasospasm is not well understood, and usual treatments have no sufficient therapeutic effects [6-9]. 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. Increased plasma and cerebrospinal fluid (CSF) level of inflammatory markers, like TNF-α, and various interleukins during SAH is seen, and this increment is correlated with poor neurological outcome [10-12]. Moreover, the systemic inflammatory response syndrome (SIRS) is associated with poor outcomes after SAH and is presented in up to 63 % of patients after SAH [13 14]. This becomes an impetus to evaluate the possible effectiveness of anti-inflammatory medications after SAH.

Ibuprofen is one of the NSAIDs which inhibit COX enzymes in a non-specific manner. In addition to decreasing the level of cytokines and prostaglandins, this drug also prevents the expression of two specific cell adhesion molecules, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) that belongs to the immunoglobulin superfamily. The immunoglobulin superfamily proteins are up-regulated in patients who develop clinical vasospasm [11]. Leukocyte integrins bind to these proteins on endothelial cells. The immunoglobulin superfamily proteins are necessary for leukocyte-endothelial cell adhesion and leukocyte migration [15-17] (Figure 1).

Ibuprofen prevents inflammatory reactions caused by leukocytes with disrupting the process of migration.

Ibuprofen's efficacy on cerebral vasospasm has been proven in an intracranial model of rabbits when its intracranial administration initiated within 6 hours after SAH, but no effect was observed when treatment is begun later than 12 hours[18]. As the acute phase of inflammation starts 3-4 hours after the SAH[11], and ibuprofen is a fast acting NSAID; it could 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 days[11], and subsequently may reduce or prevent chronic vasospasm in the upcoming days of admission. Thus, the early administration of ibuprofen considered in this study might be a key to shut off the inflammatory cascade at the initial step (Figure 1). Furthermore, in terms of side effects, the potential of NSAIDs to induce hemorrhagic stroke has been heavily dismissed by self-reports, prescriptions databases, and large multicentered studies[19].

To date, we have found four clinical trials evaluating the efficacy of NSAIDs on vasospasm after aSAH, three of which were focused on the anti-platelet mechanism of aspirin [20-22]. The fourth study was a placebo-controlled trial that assessed the preventive effects of meloxicam during seven days after aSAH [23]. However, no clinical data are available regarding the efficacy of a fast acting oral NSAID for the administration in a narrow time interval after the occurrence of aSAH. In the current study, we sought to investigate the preventive role of ibuprofen on the vasospasm secondary to aSAH and its outcomes.

Objectives

The objective of the current pilot trial is to establish the feasibility of a larger trial by successfully recruiting 30 participants over a 12-month period and demonstrating adherence to our study protocol. Additionally, we will identify possible adverse events related to the administration of ibuprofen and determine whether its administration is superior to the standard treatment in terms of the prevention of cerebral vasospasm secondary to aSAH and its clinical outcomes.

Trial design

This pilot trial is a single center, parallel randomized 1:1, controlled, clinical trial. Health care providers (physicians, ICU nurses, residents), patients, outcome assessors, and data analysts will be blinded to treatment allocation. We followed standard protocol items recommendation for interventional trials (SPIRIT) checklist to conduct this pilot clinical trial protocol[24].

METHODS

Subjects

Inclusion criteria

1. Adult patients 18y/o and older with an aneurysmal subarachnoid hemorrhage confirmed by a brain CT scan, CT angiography, magnetic resonance angiography, or digital subtraction angiography (Figure 2).
2. Admitted to the emergency department within 12 hours of the ictus.
3. Patients must have a World Federation of Neurological Surgeons (WFNS) score of I, II, or III at the initial examination.

Exclusion criteria

1. Patients who have hypersensitivity to aspirin, ibuprofen, or other NSAIDs,
2. Previous and prolonged use of any type of NSAIDs other than aspirin,
3. History of aneurysmal re-bleeding, and active bleeding of a gastrointestinal ulcer, hemodynamic instability, pregnancy, and current consumption of antiplatelet agents such as clopidogrel and aspirin.
4. Patients with history of myocardial infarction (MI) or percutaneous coronary interventions.

Outcome measures and follow-up

The goal of the current pilot trial is to establish the feasibility of a larger trial by successfully recruiting 30 participants over a 12-month period and demonstrating adherence to our study protocol. Based on the effect estimates coming out of this pilot study, we will calculate a proper sample size for the definitive trial. Specific feasibility objectives include determining:

1. Our ability to recruit 30 participants over twelve months
2. Our ability to follow 85% of participants for three months

3. Whether at least 75% of participants comply with at least 75% of the study protocol

Objectives for the Definitive Trial

The primary research objective is:

To determine the effects of Ibuprofen versus placebo on the rate of all-cause mortality

The secondary research objectives are:

1. To assess whether the administration of ibuprofen in patients with aSAH, could prevent the occurrence of cerebral vasospasm versus placebo.
2. To determine the effects of Ibuprofen versus placebo on the occurrence of delayed cerebral ischemia.
3. To elucidate the effects of Ibuprofen versus placebo on the level of disability based on modified Rankin Scale (mRS) at three-month follow-up.

Study description

The patients will be hospitalized for at least 14 days because the maximum inflammation in the subarachnoid space occurs between days 9 to 14. Based on our institutional protocol for the management of SAH, nimodipine 60 mg every 4 hours for 21 days, appropriate fluid therapy, and phenytoin will be administrated for all patients, and microsurgical aneurysmal clipping in patients presenting with large (>50mL) intraparenchymal hematomas and middle cerebral artery aneurysms, or interventional coiling will be performed for elderly (>70 years of age) patients, in those presenting with poor-grade aSAH, and in those with aneurysms of the basilar apex [25].

In the Ibuprofen arm, eligible patients (**Supplemental digital content, part 1**) will receive Ibuprofen capsules 400mg/every 6 hours for 14 days, added to standard treatment (Figure 3). Manufactured ibuprofen capsules will be administered orally in the intervention group. This dosage is an anti-inflammatory dose of ibuprofen and placed in the middle of the therapeutic

window of this drug. In the control group, placebo capsules that are manufactured identical to the ibuprofen capsules in terms of color, size, and shape; will be ordered in the same way as the intervention group. In subjects who are lethargic or have impaired consciousness, medication and placebo will be administered through enteral tube. The criteria for the evaluation of vasospasm and the scales used for assessing disability are discussed in **Supplemental digital content, part 2**.

Randomization and Allocation

To protect the blinding and integrity of the study (**Supplemental digital content, part 3**), a statistician who is not affiliated to the research team develops the randomization plan. The statistician will generate a permuted block randomization table using an online random sequence generator with an allocation list in random order. The allocation ratio is 1:1. An independent investigator allocates participants into two groups. The allocator uses an online computer-based randomization program (http://www.randomization.com) to randomize permutation [26]. In the first step, the statistician uses Randomization.com 's pseudo-random number generator of Wichmann and Hill (1982) as modified by McLeod to specify a treatment (A or B) to each participant file numbered 1 to 30. In the second step, an independent investigator will provide a random permutation of all of the integers from the smallest to the largest by the program. The independent investigator gives a file to each participant by the order provided in the previous step. The allocator will pick up a covered, sealed envelope from a box in which sequentially numbered envelopes are shuffled. Patients will receive drug A or B according to the method of allocation mentioned above.

Sample size

Our sample size is based on the confidence interval around the proportion of complete follow-up. We will consider the pilot successful if we achieved at least 85% follow-up at three months for our primary trial outcomes. 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.

Data Management and Statistical Analysis

The analysis and reporting of results will follow the CONSORT guidelines for reporting of randomised pilot and feasibility trials[27]. Data will be collected on forms and archived in a password-protected encrypted electronic database. All recruited and randomized patients will be included in the analysis. Data analysis will be performed by a blinded investigator with treatment groups coded as A and B. All data collected will be summarised for reporting purposes using descriptive statistics.

Feasibility analysis (Primary)

Data will be collected on forms and archived in a password-protected encrypted electronic database. Point estimates of recruitment and feasibility events, including adherence to protocol and follow-up rate at three months, will be presented as proportions with 95% CIs. The pilot study results will be evaluated to identify recruitment issues, data management issues, and inform anticipated follow-up rates.

Efficacy Analysis for Definitive Study (Secondary)

We plan to include the data from our pilot in the definitive trial if we can demonstrate feasibility, assuming no important changes to our patient population, intervention, or outcome measures. All patients enrolled in the trial and randomised will be included in the analysis, regardless of the level of adherence to the intervention or any other deviation from the protocol. Due to the low power of the pilot study, we will report the descriptive results for all efficacy- and harm-related outcomes. We will not complete any subgroup, sensitivity, or interim analysis due to the small sample size.

Quality Assurance

The principal investigator along with a member of institutional ethics committee will systematically monitor and evaluate the various aspects of project to ensure standards of quality are met. Standards of quality include Good Clinical Practice Guidelines, ethical conduct for Research, study protocol and institutional policies. All investigators will participate in a training session before the commencement of the study to ensure about the consistency of data collection and study procedures. Data will be managed in a secured computer system by a dedicated neurosurgery resident under the supervision of the principal investigator. In case of any doubt or uncertainty about data forms, the site investigators will be informed.

Also, for further assurance, multiple checkpoints are defined during the trial, including the presence of signed informed consents obtained by the neurosurgery residents, respect of the inclusion and exclusion criteria, appropriate and instant reporting of any adverse events, and the monitoring of all steps of the follow-up. All the files and data will be sealed and archived in a secure place at the end of the trial, once the final analysis is completed.

Trial Status

The trial is in the recruitment phase and patient enrolment is planned to be completed in March 2022, and the last recruited patient will be due for final outcome assessment in June 2022.

Safety Considerations

Concerning complications of NSAIDs, patients are classified into three categories: low, moderate, and high risk[28]. Low-risk patients are younger than 65 years without any cardiovascular risk factors. Moderate-risk patients are those 65 years of age or older without a history of gastrointestinal ulcer and had mild cardiovascular risk factors. Patients who are over 65 years old who have kidney or liver diseases or hypertension, having a history of a gastrointestinal ulcer or multiple gastrointestinal risk factors, history of cardiovascular diseases and consume aspirin or other antiplatelets as secondary prevention, as well as having a history of heart failure are considered as a high-risk patient[28]. In the first group, routine care will be provided. Pantoprazole is given in a moderate risk group along with ibuprofen. In this group, a low dose aspirin (75 to 81 mg) will be administered in case of previous consumption, and it is given with a two-hour gap after taking one of the doses of ibuprofen. Likewise, pantoprazole is given in the high-risk group if the patient did not take antiplatelet medications, such as clopidogrel. In this group, blood pressure, urea, creatinine, and electrolytes will be monitored. Thus, all patients in the three groups receive ibuprofen with the same dose. The blood pressure of the patients in the moderate and high-risk groups will be monitored. Moreover, urea, creatinine, and electrolytes (sodium, potassium) of moderate-risk patients will be measured every three days, while the same tests will be requested for the high-risk group every day [28].

Four comprehensive sections regarding the management and reporting of major adverse events are provided in the **Supplemental digital content, parts 4, 5, and 6**.

Follow-up

The clinical team will do in person follow up with the patients every day for any adverse events during initial admission and weekly for the first three weeks if discharged. A 3- month in person visit or phone interview is arranged for the assessment of disability outcomes and possible adverse events. Contact information will be available for the enrolled patients for questions or possible adverse event reports during the study period.

Expected Outcomes of the study

The key expected result of this pilot study is the feasibility and safety assessment of the administration of Ibuprofen in patients with aSAH. The objectives of the definitive trial are mentioned in the methods section. During the pilot trial, we will collect information on all outcomes for the definitive trial.

Duration of the Project

This project is scheduled to last 24 months. First patient recruited at June 2020 and the last one is planned to be included by March 2022, the end of the follow-up period for the last patient would be June 2022.

Project Management

Principal investigator: Oversight of all study procedures and managing the relations with the source of funding.

Research scientist: Study design, drafting of the proposal, RCT registration, drafting of the manuscript.

Study coordinator: Blinding, randomization of the participants, organizing datasheets, coordinating members of the team.

Neurosurgery residents: Check patients' eligibility, consenting, assessing clinical DCI, diagnosing, and managing of the adverse events, order TCD, and Ibuprofen.

Neurologist: A clinical stroke fellow will do the TCD.

Statistician: Assistance regarding study design, revising the manuscript, data analysis.

Ethics and dissemination

This study is approved by Mashhad University of Medical Sciences (MUMS) ethical committee (IR.MUMS.MEDICAL.REC.1398.225). Written informed consent will be obtained from the eligible patients or next of kin for enrollment to the study.

Dissemination policy

Results from the study will be submitted for publication regardless of whether or not there are significant findings. Every attempt will be made to ensure that the amount of time between completing data collection and the release of study findings is minimized. The Methods Centre will also be responsible for reporting required results on the ISRCTN registry.

Patient and public involvement

Patients and public were not involved in this study.

DISCUSSION

Cerebral vasospasm is a common devastating complication of the aSAH. Pharmacological management of this clinical problem is still a controversial issue.

We have found some pieces of evidence through in vitro [29], animal [18 30], and human [31 32] studies indicating that some NSAIDs might be a promising choice to be used as a repurposing approved agent for the prevention of cerebral vasospasm secondary to aSAH.

In a propensity score-matched analysis study by Nassiri et al. [31], consumption of NSAIDs with various therapeutic indications was assessed in patients with aSAH. Results demonstrated a reduction in mortality and improved functional outcomes [24]. These effects were independent of the development of DCI or vasospasm. Furthermore, patients treated with NSAIDs had reduced ICU and hospital stay. The authors hypothesized that inflammation may have a critical role in development of poor outcomes (disability and death) after aSAH and patients with aSAH may find some benefit from NSAIDs.

A large, high-quality trial is needed to establish whether adding ibuprofen to standard treatment effectively reduces vasospasm after aSAH. Such a 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.

Ibuprofen is an FDA-approved anti-inflammatory medication; however, using it in a new clinical condition as a repurposing approved agent to prevent cerebral vasospasm requires further evaluation. Since there is no previous phase III trial for this purpose, we planned to run feasibility pilot study before the definitive trial.

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Authors contribution

SZ and MD conceptualized the study. MD, EM, VA, and BS designed the study, EM and MJY coordinated the administrative tasks. EM, MD did the literature search, and drafted the initial version of the manuscript. MD designed the concept map and all figures. JG, NG, and SZ and all authors critically reviewed and approved the final manuscript as submitted.

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Declaration of interests

All authors declare no conflict of interest.

Figures and legends

Figure 1: Concept map depicting four major pathways for the occurrence of cerebral vasospasm following aSAH. Inflammatory pathway is shown in yellow and explains how Ibuprofen may act as a prophylactic agent in this scenario. Numbers in parentheses are representative of corresponding reference for that branch, all concept map references are available in **Supplemental digital content, part 7**.

Figure 2. Step-by-step flow diagram of the study

Figure 3. Timeline of the study

Supplemental Digital Content (SDC) #. Medium. Title.

SDC, part 1, Text, Enrolment

SDC, part 2, Text, Criteria for the evaluation of vasospasm and disability

SDC, part 3, Text, Blinding

SDC, part 4, Text, Adverse events definition

SDC, part 5, Text, Serious adverse events

SDC, part 6, Text, Adverse Event (AE) Reporting

SDC, part 7, Text, References of the concept map

SDC, part 8, Text, References for supplementary text

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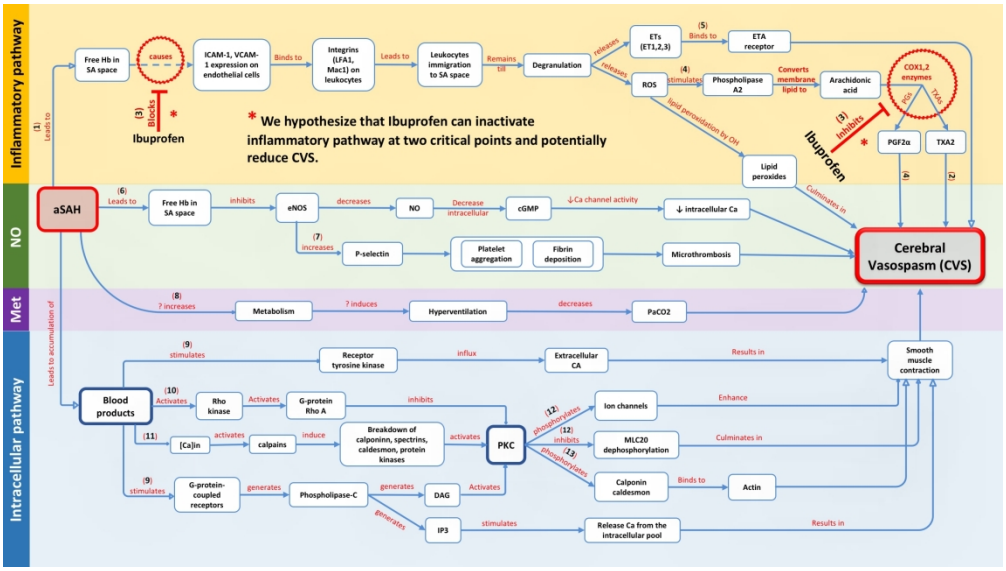


Figure 1. Concept map depicting four major pathways for the occurrence of cerebral vasospasm following aSAH. Inflammatory pathway is shown in yellow and explains how Ibuprofen may act as a prophylactic agent in this scenario. Numbers in parentheses are representative of corresponding reference for that branch, all concept map references are available in Supplemental digital content, part 7.

1057x595mm (72 x 72 DPI)

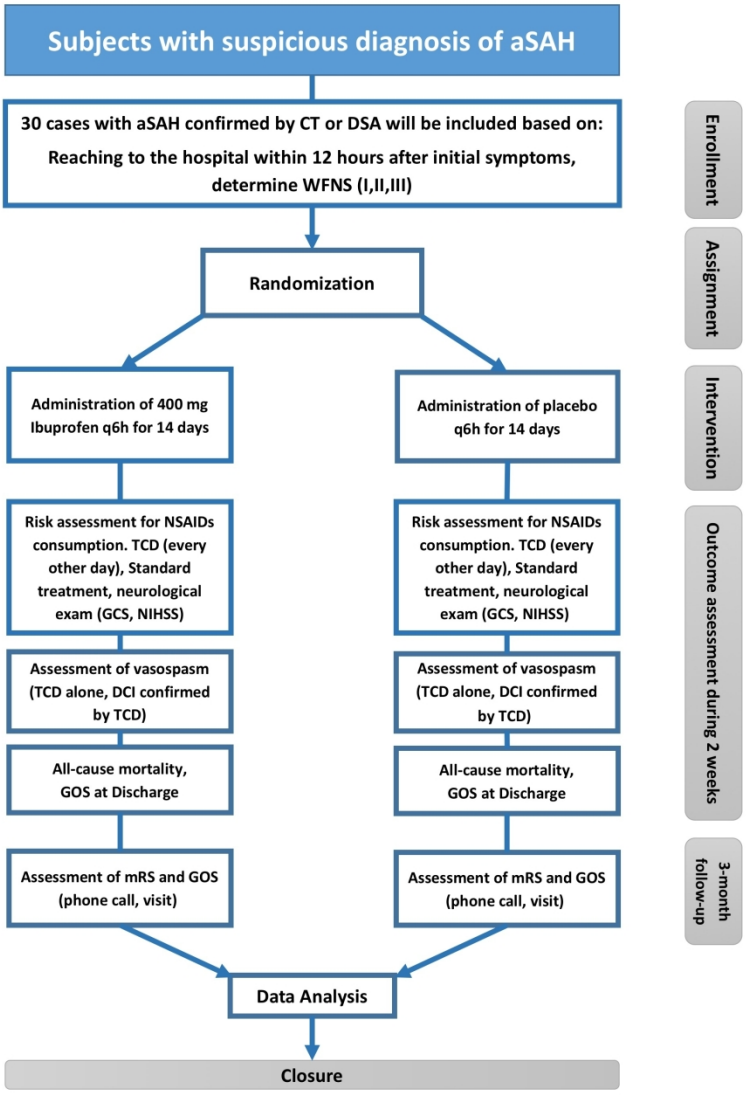
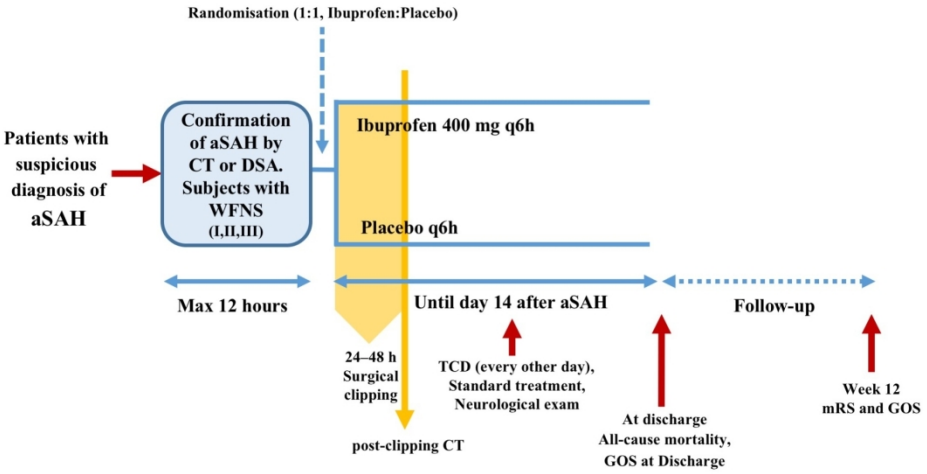


Figure 2. Step-by-step flow diagram of the study

190x254mm (300 x 300 DPI)



Timeline of the study

703x386mm (72 x 72 DPI)

Supplemental digital content (SDC)

Prophylactic effects of Ibuprofen on cerebral vasospasm following aneurysmal subarachnoid hemorrhage: Protocol for a randomised placebo-controlled pilot trial

Authors:

Mojtaba Dayyani[1, 2] Ermia Mousavi Mohammadi[2], Vahid Ashoorion[3], Behnam Sadeghirad[3], Mohammadreza javedani yekta[2], James Grotta[4], Nestor Gonzalez[5], Samira Zabihiyan[2, *]

Table of Contents

SDC, part 1. Enrolment

Patient screening for eligibility and recruitment will be conducted at Ghaem Teaching Hospital, Mashhad, Iran. Two neurosurgery residents will first visit the patients and check the eligibility criteria in the emergency department. The neurosurgical intensive care unit of our center annually receives 100–150 patients with aSAH. Over twelve months, 30 eligible patients will be enrolled in our trial.

The recruited patient who met the criteria will sign and date the institutional informed consent form of the Mashhad University of Medical Sciences before allocating to each group and before initiation of any procedures related to the clinical investigation are performed. Then, required data will be gathered in specific datasheets, including demographic data (name, age, gender, address, and phone number), past medical history including cardiovascular, kidney, and liver diseases, previous episode of SAH, drug history including long term and recent use of any NSAIDs, anti-platelet medications and sensitivity to aspirin or any NSAIDs. Two nurses of the hospital's intensive care unit will fill case report forms (CRFs) and gather these data. In the absence of exclusion criteria, a file will be specified to each patient that contains a registration form, consent form, diagnostic form, and a 3-months follow-up evaluation sheet.

CRFs will be kept in a file that assigns to each patient. The research coordinator enters data from forms to a data management tool. Only the research coordinator has access to data in a password-protected spreadsheet till the study will be terminated. After this period, the research coordinator will send the spreadsheet to the method center located in the hospital. Also, to assess the patients' disability, a 3-months follow-up will be accomplished via a phone call or a clinic visit by two independent neurosurgery residents.

Participants who are unable to complete the protocol due to death, clinical complication, or being discharged for any reason will not be excluded from the study. The statisticians will apply the intention to treat analysis.

SDC, part 2. Criteria for the evaluation of vasospasm and disability

Chronic vasospasm can occur clinically with signs and symptoms or non-clinically that would be diagnosed by imaging [1]. In this study, we defined clinical vasospasm as delayed cerebral ischemia (DCI) and diagnosed non-clinically by Transcranial Doppler (TCD). The flow velocity of the

middle cerebral artery (MCA) and the basilar artery is measured by TCD at the admission, then every two days. The timeline of the interventions is depicted in figure 3. In MCA, the flow velocity between 120-149 cm/s and Lindegaard ratio 3 to 6 was considered as mild vasospasm (25% vessel obstruction), velocity between 150-199 cm/s and Lindegaard ratio 3 to 6 as moderate vasospasm (50% obstruction) and a velocity more than or equal to 200 cm/s and a Lindegaard ratio greater than 6 as severe vasospasm (more than 50% occlusion). In the basilar artery, the flow velocity between 70-85 cm/s and Lindegaard ratio 2 to 2.49 was considered as mild vasospasm (25% vessel obstruction), the velocity greater than 85 cm/s, and Lindegaard ratio between 2.5 to 2.99 as moderate vasospasm (50% obstruction) and a velocity over 85 cm/s and the Lindegaard ratio greater than or equal to 3 as severe vasospasm (more than 50% obstruction) [2]. DCI is considered if the patient's neurological status deteriorates for at least 2 hours, and no reasons were found. The neurological deterioration is defined as one or more decrement of the Glasgow Coma Scale (GCS) score or increases at least two scores of the National Institutes of Health Stroke Scale (NIHSS) [3]; in this condition, vasospasm will be confirmed by TCD.

Disability will be assessed at discharge and three months after discharge based on the Modified Rankin Scale (mRS). Favorable mRS outcomes are (mRS 1 and 2), and unfavorable outcomes are (mRS 3 to 6).

SDC, part 3. Blinding

Participants of both groups will be blinded to take their correspondent medication or placebo. Also, ibuprofen and placebo will be packed in identical capsules, and they are not distinguishable by participants or study personnel.

The clinical team, including neurosurgeons, radiologists and, ICU department staff, and the neurologist who does TCD, are not aware of which group patients belong to. Outcomes will be recorded in a list based on patient allocation to either group A or B. Likewise, the statistician would not be aware of what data belongs to either the intervention or placebo groups in the final datasheet. Breaking of the treatment codes will be carried out three months after the inclusion of the last eligible patient. All outcome assessments will be performed before the treatment codes are broken.

SDC, part 4. Adverse events definition

Oral administration of ibuprofen has some common adverse reactions that their prevalence is ranged between 1-10%. In these conditions, it is not necessary to discontinue drug consumption. Edema due to fluid retention occurs in 1 to 3%. Central nervous system reactions included dizziness (3-9%), headache (1-3%), and nervousness (1-3%). Skin rashes (3-9%) and pruritus (1-3%) are dermatologic reactions that may occur by ibuprofen consumption. There are some adverse events in the gastrointestinal system which may arise from ibuprofen, including epigastric pain (3-9%), heartburn (3-9%), nausea (3-9%), abdominal pain (1-3%), constipation (1-3%), decreased appetite (1-3%), diarrhea (1-3%), dyspepsia (1-3%), vomiting (1-3%). Tinnitus is the otic complications which may happen by the prevalence of 3-9% [5].

SDC, part 5. Serious adverse events

The first possible serious adverse events are cardiovascular thrombotic events, including myocardial infarction (MI). Another serious cardiovascular event is new-onset hypertension or exacerbation of hypertension [6]. We will strictly monitor blood pressure as a part of our routine management in the ICU, which helps us detect this event before its remarkable increment.

In general, using the lowest effective dose for the shortest duration of time might reduce the risk of cardiovascular events. In our study, these conditions are considered. In case of any clinical suspicion for MI, in the initial assessment phase, a 12-lead ECG, an abbreviated history, and physical examination will obtain within 10 minutes [7]. Then, the serum level of Troponin-I will be measured, and cardiology consultation will be requested for further evaluation or possible therapeutic interventions.

Gastrointestinal events, including an increased risk of ulceration, bleeding, and perforation, are the second possible serious adverse events. Elderly patients and patients with a history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [8]. We avoid enrolling patients with a history of acute GI bleeding. Concomitant gastro-protective therapy (e.g., proton pump inhibitors (PPIs) [9] is recommended; as mentioned in the safety section, we use PPIs for all study participants. For the initial evaluation of the patient with the signs of active upper GI bleeding, hemodynamic stability, and the necessity for fluid resuscitation will be assessed. Intravenous pantoprazole at the dose of 40 mg twice daily will be initiated for these patients [10].

Endoscopy within 24 hours of presentation for the diagnosis and treatment of active upper GI bleeding will be accomplished [11].

The third serious adverse event secondary to ibuprofen use is the accentuation of existing renal dysfunction that is dose-dependent [9]. The proposed criteria for acute kidney injury[12] include an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or an increase to ≥1.5 times the presumed baseline value that is known to have occurred within the last seven days or a decrease in urine volume to <3 mL/kg over six hours [13]. The diagnosis of hemodynamically mediated AKI associated with NSAIDs is suggested by recent NSAID use, the absence of significant proteinuria (<500 mg/day), hematuria, and the bland urine sediment. Among patients with AKI, generally, a renal ultrasound will be done to exclude possible obstruction. In general, the diagnosis is made when kidney function recovery occurs after the NSAID is discontinued [14]. For the treatment of NSAID-induced AKI, the NSAID should be stopped immediately, volume resuscitation will be provided in states of hypovolemia and continued based on a reassessment of volume status including blood pressure/pulse and urine output [15].

The fourth serious adverse event is anaphylactic reactions. The most common signs and symptoms are cutaneous (e.g. sudden onset of generalized urticarial, angioedema, flushing, and pruritus). Airway will be assessed at first [16]. Epinephrine will be given 0.3 to 0.5 mg intramuscularly (IM), which can be repeated every 5 to 15 minutes. Oxygen will be given 8-10 L/min via face mask as needed. Hypotension, if occurs, will be managed via rapid infusion of 1 to 2 liters intravenously. Adjunctive therapies including IV diphenhydramine 25 to 50 mg, IV ranitidine 50 mg, IV methylprednisolone 125 mg, and monitoring hemodynamic, pulse oximetry, and urine output will be considered as appropriate [17-19].

Unanticipated problems resulting in risk to participant or others

Any incident, experience, or outcome that meets the following criteria:

- Unexpected in nature, severity, or frequency (e.g., not described in study-related documents such as the ethics-approved protocol or consent form, etc.).
- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience or outcome may have been caused by the procedures involved in the research), and suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm)

SDC, part 6. Adverse Event (AE) Reporting

The clinical site (ICU nurse and neurosurgery resident) is responsible for reporting AEs to the Methods Centre promptly. Significant new information on ongoing AEs should also be provided promptly to the Methods Centre via the data capture system. Unanticipated problems resulting in risk to participants or others are also to be reported promptly to the Methods Centre.

The clinical site is responsible for reporting AEs and unanticipated problems resulting in risk to participants or others to their local ethics committee in accordance with local reporting requirements. Copies of each report and documentation of ethic board notification and receipt will be kept in the clinical site's study file. The Methods Centre will be responsible for reporting any applicable adverse events to the relevant regulatory bodies (e.g., Food and Drug organization, adverse events registration).

SDC, part 7. References of the concept map

1. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World Neurosurg.* 2010;73(1):22-41.
2. Viski S, Olah L. Use of Transcranial Doppler in Intensive Care Unit. *J Crit Care Med (Targu Mures).* 2017;3(3):99-104.
3. Nassiri F, Ibrahim GM, Badhiwala JH, et al. A Propensity Score-Matched Study of the Use of Non-steroidal Anti-inflammatory Agents Following Aneurysmal Subarachnoid Hemorrhage. *Neurocrit Care.* 2016;25(3):351-358.
4. Ibuprofen: Drug information. In: *UpToDate.*2017.
5. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. *New England Journal of Medicine.* 1991;324(24):1716-1725.
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-2035.
7. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology.* 2008;52(18):1502-1517.
8. Huerta C, Castellsague J, Varas-Lorenzo C, Rodríguez LAG. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *American Journal of Kidney Diseases.* 2005;45(3):531-539.
9. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA internal medicine.* 2014;174(11):1755-1762.

10. Marmo R, Rotondano G, Piscopo R, Bianco MA, D'angella R, Cipolletta L. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. *The American journal of gastroenterology.* 2007;102(2):279.
11. Shiba M, Suzuki H, Fujimoto M, et al. Role of platelet-derived growth factor in cerebral vasospasm after subarachnoid hemorrhage in rats. *Acta Neurochir Suppl.* 2013;115:219-223.
12. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of the American Society of Nephrology.* 2005;16(11):3365-3370.
13. Whelton A, Stout RL, Spilman PS, Klassen DK. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure: a prospective, randomized, crossover comparison. *Annals of Internal Medicine.* 1990;112(8):568-576.
14. Luciano R. NSAIDs: Acute kidney injury (acute renal failure). In: Palevsky PM, Sheridan A, eds. *UpToDate.*2017.
15. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *Journal of Allergy and Clinical Immunology.* 2007;119(4):1016.
16. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *Journal of Allergy and Clinical Immunology.* 2001;108(5):871-873.
17. Pumphrey RS. Fatal posture in anaphylactic shock. *Journal of Allergy and Clinical Immunology.* 2003;112(2):451-452.
18. Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. *Current opinion in allergy and clinical immunology.* 2010;10(4):354-361.

SDC, part 8. References for supplementary text

1. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World Neurosurg.* 2010;73(1):22-41.
2. Viski S, Olah L. Use of Transcranial Doppler in Intensive Care Unit. *J Crit Care Med (Targu Mures).* 2017;3(3):99-104.
3. Nassiri F, Ibrahim GM, Badhiwala JH, et al. A Propensity Score-Matched Study of the Use of Non-steroidal Anti-inflammatory Agents Following Aneurysmal Subarachnoid Hemorrhage. *Neurocrit Care.* 2016;25(3):351-358.
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7. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-2035.

8. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology.* 2008;52(18):1502-1517.
9. Huerta C, Castellsague J, Varas-Lorenzo C, Rodríguez LAG. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *American Journal of Kidney Diseases.* 2005;45(3):531-539.
10. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA internal medicine.* 2014;174(11):1755-1762.
11. Marmo R, Rotondano G, Piscopo R, Bianco MA, D'angella R, Cipolletta L. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. *The American journal of gastroenterology.* 2007;102(2):279.
12. Shiba M, Suzuki H, Fujimoto M, et al. Role of platelet-derived growth factor in cerebral vasospasm after subarachnoid hemorrhage in rats. *Acta Neurochir Suppl.* 2013;115:219-223.
13. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of the American Society of Nephrology.* 2005;16(11):3365-3370.
14. Whelton A, Stout RL, Spilman PS, Klassen DK. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure: a prospective, randomized, crossover comparison. *Annals of Internal Medicine.* 1990;112(8):568-576.
15. Luciano R. NSAIDs: Acute kidney injury (acute renal failure). In: Palevsky PM, Sheridan A, eds. *UpToDate.*2017.
16. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *Journal of Allergy and Clinical Immunology.* 2007;119(4):1016.
17. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *Journal of Allergy and Clinical Immunology.* 2001;108(5):871-873.
18. Pumphrey RS. Fatal posture in anaphylactic shock. *Journal of Allergy and Clinical Immunology.* 2003;112(2):451-452.
19. Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. *Current opinion in allergy and clinical immunology.* 2010;10(4):354-361.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No in the manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page and 17
	5b	Name and contact information for the trial sponsor	Title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 14, 15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	6, 9

Objectives	7	Specific objectives or hypotheses	7, 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13 and supplement 4,5, and 6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12, 14, 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9, 13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2, 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12, 14, 15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10 and supplement 3
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10 and supplement 3
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10 and supplement 3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7 and supplement 3
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11, 12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 12, 13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11, 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14, 15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13, 14 and supplement 4,5, and 6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14, 15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Title page
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11,12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Via Publication
	31b	Authorship eligibility guidelines and any intended use of professional writers	ICMJE
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Farsi
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Aneurysmal subarachnoid hemorrhage- cerebral vasospasm and prophylactic Ibuprofen: A randomised controlled pilot trial protocol

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Manuscript ID	bmjopen-2021-058895.R1
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Complete List of Authors:	Dayyani, Mojtaba; City of Hope National Medical Center, Neurosurgery Mousavi Mohammadi , Ermia ; Mashhad University of Medical Sciences Ghaem Hospital, Neurosurgery Ashoorion, Vahid; McMaster University Department of Health Research Methods Evidence and Impact Sadeghirad, Behnam; McMaster University Department of Health Research Methods Evidence and Impact Javedani Yekta , Mohammadreza ; Mashhad University of Medical Sciences Ghaem Hospital Grotta, James; Memorial Hermann Texas Medical Center Gonzalez, Nestor; Cedars-Sinai Medical Center, Neurosurgery Zabihyan, Samira; Mashhad University of Medical Sciences Ghaem Hospital, Neurosurgery
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Intensive care, Research methods
Keywords:	Stroke < NEUROLOGY, NEUROSURGERY, Clinical trials < THERAPEUTICS

Aneurysmal subarachnoid hemorrhage- cerebral vasospasm and prophylactic Ibuprofen: A randomised controlled pilot trial protocol

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List of Abbreviations

Abbreviation	Explanation
aSAH	aneurysmal Subarachnoid Hemorrhage
CI	Confidence Interval
COX	Cyclooxygenase
CSF	Cerebrospinal Fluid
CTA	CT Angiography
CVS	Cerebral Vasospasm
DSA	Digital Subtraction Angiography
ICAM-1	Intercellular adhesion molecule-1
ICU	Intensive care unit
TCD	Transcranial Doppler
MRA	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
PSVMCA	Peak Systolic Middle Cerebral Artery Velocity
SIRS	Systemic Inflammatory Response Syndrome
SPIRIT	Standard Protocol Items Recommendation for Interventional Trials
TXA	Thromboxane
VCAM-1	Vascular Cell Adhesion Molecule-1
WFNS	World Federation of Neurological Surgeons

Abstract

Introduction: Cerebral vasospasm (CVS) is the leading cause of mortality and morbidity following aSAH. One of the recently implicated underlying mechanisms of CVS is inflammatory cascades. Specific feasibility objectives include determining the ability to recruit 30 participants over twelve months while at least 75% of them comply with at least 75% of the study protocol and being able to follow 85% of them for three months after discharge.

Methods and analysis: This is a feasibility study for a randomised, controlled trial. Eligible participants are adult patients 18y/o and older with an aSAH confirmed by a brain CT scan, and CT angiography, or magnetic resonance angiography, or digital subtraction angiography who admitted to the emergency department within 12 hours of the ictus. Eligible subjects will be randomised 1:1 for the administration of either ibuprofen or a placebo, while both groups will concomitantly be treated by the standard of care for two weeks. Care givers, patients, outcome assessors and data analysts will be blinded. This will be the first study to investigate the preventive effects of a short acting NSAID on CVS and the key expected outcome of this pilot study is the feasibility and safety assessment of the administration of Ibuprofen in patients with aSAH. The objectives of the definitive trial would be to assess the effect of Ibuprofen relative to placebo on mortality, CVS, DCI, and level of disability at 3-month follow-up.

Ethics and dissemination: This study is approved by Mashhad University of Medical Sciences ethical committee (IR.MUMS.MEDICAL.REC.1398.225). Results from the study will be submitted for publication regardless of whether or not there are significant findings.

Trial registration: ISRCTN14611625

Keywords: Aneurysmal subarachnoid hemorrhage, Cerebral vasospasm, Delayed cerebral ischemia, Feasibility study, Ibuprofen, Randomised Controlled Trial.

Strengths and limitations of this study

- Rigorous trial protocol to evaluate the feasibility and safety of conducting a larger phase III trial to assess the preventive role of Ibuprofen on cerebral vasospasm secondary to aneurysmal Subarachnoid Hemorrhage (aSAH).
- Based on this feasibility pilot trial, four critical outcomes will be evaluated in the definitive trial including mortality, cerebral vasospasm, DCI, and level of disability at 3-month follow-up.
- Recruitment of eligible participants in a narrow time window (12-hour) after the occurrence of aSAH is a challenging inclusion criteria that may slows down the advancement of the trial.
- To minimize any potential bias, blinding of health care providers (physicians, ICU nurses, residents), patients, outcome assessors, and data analysts to treatment allocation is being undertaken.
- Example of a low cost trial due to using a repurposed FDA approved and affordable agent as prophylactic therapy.

INTRODUCTION

Background and Rationale

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 5–10 % of all strokes worldwide, which approximately equals to a total of 600,000 new cases per year [1]. Up to 44% of such cases will die [2], and almost 20% of the survived ones would become disabled and dependent [2]. Cerebral vasospasm following aSAH is the leading cause of mortality and morbidity [3-5]. The exact mechanisms of the complex inflammatory cascade leading to cerebral vasospasm is not well understood, and usual treatments have no sufficient therapeutic effects [6-9]. 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. Increased plasma and cerebrospinal fluid (CSF) level of inflammatory markers, like TNF-α, and various interleukins during SAH is seen, and this increment is correlated with poor neurological outcome [10-12]. Moreover, the systemic inflammatory response syndrome (SIRS) is associated with poor outcomes after SAH and is presented in up to 63 % of patients after SAH [13 14]. This becomes an impetus to evaluate the possible effectiveness of anti-inflammatory medications after SAH.

Ibuprofen is one of the NSAIDs which inhibit COX enzymes in a non-specific manner. In addition to decreasing the level of cytokines and prostaglandins, this drug also prevents the expression of two specific cell adhesion molecules, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) that belongs to the immunoglobulin superfamily. The immunoglobulin superfamily proteins are up-regulated in patients who develop clinical vasospasm [11]. Leukocyte integrins bind to these proteins on endothelial cells. The immunoglobulin superfamily proteins are necessary for leukocyte-endothelial cell adhesion and leukocyte migration [15-17] (Figure 1, **Supplemental digital content, part 1**).

Ibuprofen prevents inflammatory reactions caused by leukocytes with disrupting the process of migration.

Ibuprofen's efficacy on cerebral vasospasm has been proven in an intracranial model of rabbits when its intracranial administration initiated within 6 hours after SAH, but no effect was observed when treatment is begun later than 12 hours[18]. As the acute phase of inflammation starts 3-4 hours after the SAH[11], and ibuprofen is a fast acting NSAID; it could 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 days[11], and subsequently may reduce or prevent chronic vasospasm in the upcoming days of admission. Thus, the early administration of ibuprofen considered in this study might be a key to shut off the inflammatory cascade at the initial step (Figure 1). Furthermore, in terms of side effects, the potential of NSAIDs to induce hemorrhagic stroke has been heavily dismissed by self-reports, prescriptions databases, and large multicentered studies[19].

To date, we have found four clinical trials evaluating the efficacy of NSAIDs on vasospasm after aSAH, three of which were focused on the anti-platelet mechanism of aspirin [20-22]. The fourth study was a placebo-controlled trial that assessed the preventive effects of meloxicam during seven days after aSAH [23]. However, no clinical data are available regarding the efficacy of a fast acting oral NSAID for the administration in a narrow time interval after the occurrence of aSAH. In the current study, we sought to investigate the preventive role of ibuprofen on the vasospasm secondary to aSAH and its outcomes.

Objectives

The objective of the current pilot trial is to establish the feasibility of a larger trial by successfully recruiting 30 participants over a 12-month period and demonstrating adherence to our study protocol. Additionally, we will identify possible adverse events related to the administration of ibuprofen and determine whether its administration is superior to the standard treatment in terms of the prevention of cerebral vasospasm secondary to aSAH and its clinical outcomes.

Trial design

This pilot trial is a single center, parallel randomized 1:1, controlled, clinical trial. Health care providers (physicians, ICU nurses, residents), patients, outcome assessors, and data analysts will be blinded to treatment allocation. We followed standard protocol items recommendation for interventional trials (SPIRIT) checklist to conduct this pilot clinical trial protocol[24].

METHODS

Subjects

Inclusion criteria

1. Adult patients 18y/o and older with an aneurysmal subarachnoid hemorrhage confirmed by a brain CT scan, and CT angiography, or magnetic resonance angiography, or digital subtraction angiography (Figure 2).
2. Admitted to the emergency department within 12 hours of the ictus.
3. Patients must have a World Federation of Neurological Surgeons (WFNS) score of I, II, or III at the initial examination.

Exclusion criteria

1. Patients who have hypersensitivity to aspirin, ibuprofen, or other NSAIDs,
2. Previous and prolonged use of any type of NSAIDs,
3. History of aneurysmal re-bleeding, and active bleeding of a gastrointestinal ulcer, hemodynamic instability, pregnancy, and current consumption of antiplatelet agents such as clopidogrel and aspirin.
4. Patients with history of myocardial infarction (MI) or percutaneous coronary interventions.

Outcome measures and follow-up

The goal of the current pilot trial is to establish the feasibility of a larger trial by successfully recruiting 30 participants over a 12-month period and demonstrating adherence to our study protocol. Based on the effect estimates coming out of this pilot study, we will calculate a proper sample size for the definitive trial. Specific feasibility objectives include determining:

1. Our ability to recruit 30 participants over twelve months
2. Our ability to follow 85% of participants for three months

3. Whether at least 75% of participants comply with at least 75% of the study protocol

Objectives for the Definitive Trial

The primary research objective is:

To determine the effects of Ibuprofen versus placebo on the rate of all-cause mortality

The secondary research objectives are:

1. To assess whether the administration of ibuprofen in patients with aSAH, could prevent the occurrence of cerebral vasospasm versus placebo.
2. To determine the effects of Ibuprofen versus placebo on the occurrence of delayed cerebral ischemia.
3. To elucidate the effects of Ibuprofen versus placebo on the level of disability based on modified Rankin Scale (mRS) at three-month follow-up.

Study description

The patients will be hospitalized for at least 14 days because the maximum inflammation in the subarachnoid space occurs between days 9 to 14. Based on our institutional protocol for the management of SAH, nimodipine 60 mg every 4 hours for 21 days, appropriate fluid therapy, and phenytoin will be administrated for all patients, and microsurgical aneurysmal clipping in patients presenting with large (>50mL) intraparenchymal hematomas and middle cerebral artery aneurysms, or interventional coiling will be performed for elderly (>70 years of age) patients, in those presenting with poor-grade aSAH, and in those with aneurysms of the basilar apex [25].

In the Ibuprofen arm, eligible patients (**Supplemental digital content, part 2**) will receive Ibuprofen capsules 400mg/every 6 hours for 14 days, added to standard treatment (Figure 3). Manufactured ibuprofen capsules will be administered orally in the intervention group. This dosage is an anti-inflammatory dose of ibuprofen and placed in the middle of the therapeutic

window of this drug. In the control group, placebo capsules that are manufactured identical to the ibuprofen capsules in terms of color, size, and shape; will be ordered in the same way as the intervention group. In subjects who are lethargic or have impaired consciousness, medication and placebo will be administered through enteral tube. The criteria for the evaluation of vasospasm and the scales used for assessing disability are discussed in **Supplemental digital content, part 3**.

Randomization and Allocation

To protect the blinding and integrity of the study (**Supplemental digital content, part 4**), a statistician who is not affiliated to the research team develops the randomization plan. The statistician will generate a permuted block randomization table using an online random sequence generator with an allocation list in random order. The allocation ratio is 1:1. An independent investigator allocates participants into two groups. The allocator uses an online computer-based randomization program (http://www.randomization.com) to randomize permutation [26]. In the first step, the statistician uses Randomization.com's pseudo-random number generator of Wichmann and Hill (1982) as modified by McLeod to specify a treatment (A or B) to each participant file numbered 1 to 30. In the second step, an independent investigator will provide a random permutation of all of the integers from the smallest to the largest by the program. The independent investigator gives a file to each participant by the order provided in the previous step. The allocator will pick up a covered, sealed envelope from a box in which sequentially numbered envelopes are shuffled. Patients will receive drug A or B according to the method of allocation mentioned above.

Sample size

Our sample size is based on the confidence interval around the proportion of complete follow-up. We will consider the pilot successful if we achieved at least 85% follow-up at three months for our primary trial outcomes. 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.

Data Management and Statistical Analysis

The analysis and reporting of results will follow the CONSORT guidelines for reporting of randomised pilot and feasibility trials[27]. Data will be collected on forms and archived in a password-protected encrypted electronic database. All recruited and randomized patients will be included in the analysis. Data analysis will be performed by a blinded investigator with treatment groups coded as A and B. All data collected will be summarised for reporting purposes using descriptive statistics.

Feasibility analysis (Primary)

Data will be collected on forms and archived in a password-protected encrypted electronic database. Point estimates of recruitment and feasibility events, including adherence to protocol and follow-up rate at three months, will be presented as proportions with 95% CIs. The pilot study results will be evaluated to identify recruitment issues, data management issues, and inform anticipated follow-up rates.

Efficacy Analysis for Definitive Study (Secondary)

We plan to include the data from our pilot in the definitive trial if we can demonstrate feasibility, assuming no important changes to our patient population, intervention, or outcome measures. All patients enrolled in the trial and randomised will be included in the analysis, regardless of the level of adherence to the intervention or any other deviation from the protocol. Due to the low power of the pilot study, we will report the descriptive results for all efficacy- and harm-related outcomes. We will not complete any subgroup, sensitivity, or interim analysis due to the small sample size.

Quality Assurance

The principal investigator along with a member of institutional ethics committee will systematically monitor and evaluate the various aspects of project to ensure standards of quality are met. Standards of quality include Good Clinical Practice Guidelines, ethical conduct for Research, study protocol and institutional policies. All investigators will participate in a training session before the commencement of the study to ensure about the consistency of data collection and study procedures. Data will be managed in a secured computer system by a dedicated neurosurgery resident under the supervision of the principal investigator. In case of any doubt or uncertainty about data forms, the site investigators will be informed.

Also, for further assurance, multiple checkpoints are defined during the trial, including the presence of signed informed consents obtained by the neurosurgery residents, respect of the inclusion and exclusion criteria, appropriate and instant reporting of any adverse events, and the monitoring of all steps of the follow-up. All the files and data will be sealed and archived in a secure place at the end of the trial, once the final analysis is completed.

Trial Status

The trial is in the recruitment phase and patient enrolment is planned to be completed in April 2022, and the last recruited patient will be due for final outcome assessment in July 2022.

Safety Considerations

Concerning complications of NSAIDs, patients are classified into three categories: low, moderate, and high risk[28]. Low-risk patients are younger than 65 years without any cardiovascular risk factors. Moderate-risk patients are those 65 years of age or older without a history of gastrointestinal ulcer and had mild cardiovascular risk factors. Patients who are over 65 years old who have kidney or liver diseases or hypertension, having a history of a gastrointestinal ulcer or multiple gastrointestinal risk factors, history of cardiovascular diseases, as well as having a history of heart failure are considered as a high-risk patient[28]. In the first group, routine care will be provided. Pantoprazole is administered in the moderate risk and high-risk group along with ibuprofen. We strictly monitor blood pressure as a part of our routine management of all patients in ICU. Moreover, urea, creatinine, and electrolytes (sodium, potassium) of moderate-risk patients will be measured every three days, while the same tests will be requested for the high-risk group every day [28]. 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.

Based on the recommendation of extension of the CONSORT statement on better reporting of harms in randomized trials[27 29], 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 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 them among the participants, we will use the Table for Grading the Severity of Adult and Pediatric Adverse Events.[30]" Four comprehensive sections regarding the management and reporting adverse events are provided in the **Supplemental digital content, parts 5, 6, 7, and 8**.

Follow-up

The clinical team will do in person follow up with the patients every day for any adverse events during initial admission and weekly for the first three weeks if discharged. A 3- month in person visit or phone interview is arranged for the assessment of disability outcomes and possible adverse events. Contact information will be available for the enrolled patients for questions or possible adverse event reports during the study period.

Expected Outcomes of the study

The key expected result of this pilot study is the feasibility and safety assessment of the administration of Ibuprofen in patients with aSAH. The objectives of the definitive trial are mentioned in the methods section. During the pilot trial, we will collect information on all outcomes for the definitive trial.

Duration of the Project

This project is scheduled to last 24 months. First patient recruited at June 2020 and the last one is planned to be included by April 2022, the end of the follow-up period for the last patient would be July 2022.

Project Management

Principal investigator: Oversight of all study procedures and managing the relations with the source of funding.

Research scientist: Study design, drafting of the proposal, RCT registration, drafting of the manuscript.

Study coordinator: Blinding, randomization of the participants, organizing datasheets, coordinating members of the team.

Neurosurgery residents: Check patients' eligibility, consenting, assessing clinical DCI, diagnosing, and managing of the adverse events, order TCD, and Ibuprofen.

Neurologist: A clinical stroke fellow will do the TCD.

Statistician: Assistance regarding study design, revising the manuscript, data analysis.

Ethics and dissemination

This study is approved by Mashhad University of Medical Sciences (MUMS) ethical committee (IR.MUMS.MEDICAL.REC.1398.225). Written informed consent will be obtained from the eligible patients or next of kin for enrollment to the study.

Dissemination policy

Results from the study will be submitted for publication regardless of whether or not there are significant findings. Every attempt will be made to ensure that the amount of time between

completing data collection and the release of study findings is minimized. The Methods Centre will also be responsible for reporting required results on the ISRCTN registry.

Patient and public involvement

Patients and public were not involved in this study.

DISCUSSION

Cerebral vasospasm is a common devastating complication of the aSAH. Pharmacological management of this clinical problem is still a controversial issue.

We have found some pieces of evidence through in vitro [31], animal [18 32], and human [33 34] studies indicating that some NSAIDs might be a promising choice to be used as a repurposing approved agent for the prevention of cerebral vasospasm secondary to aSAH.

In a propensity score-matched analysis study by Nassiri et al. [33], consumption of NSAIDs with various therapeutic indications was assessed in patients with aSAH. Results demonstrated a reduction in mortality and improved functional outcomes [24]. These effects were independent of the development of DCI or vasospasm. Furthermore, patients treated with NSAIDs had reduced ICU and hospital stay. The authors hypothesized that inflammation may have a critical role in development of poor outcomes (disability and death) after aSAH and patients with aSAH may find some benefit from NSAIDs.

A large, high-quality trial is needed to establish whether adding ibuprofen to standard treatment effectively reduces vasospasm after aSAH. Such a 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.

Ibuprofen is an FDA-approved anti-inflammatory medication; however, using it in a new clinical condition as a repurposing approved agent to prevent cerebral vasospasm requires further evaluation. Since there is no previous phase III trial for this purpose, we planned to run feasibility pilot study before the definitive trial.

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Authors contribution

SZ and MD conceptualized the study. MD, EM, VA, and BS designed the study, EM and MJY coordinated the administrative tasks. EM, MD did the literature search, and drafted the initial version of the manuscript. MD designed the concept map and all figures. JG, NG, and SZ and all authors critically reviewed and approved the final manuscript as submitted.

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Declaration of interests

All authors declare no conflict of interest.

Figures and legends

Figure 1: Concept map depicting four major pathways for the occurrence of cerebral vasospasm following aSAH. Inflammatory pathway is shown in yellow and explains how Ibuprofen may act as a prophylactic agent in this scenario. Numbers in parentheses are representative of corresponding reference for that branch, all concept map references are available in **Supplemental digital content, part 1**.

ICAM-1, Intercellular Adhesion Molecule 1; VCAM, vascular cell adhesion molecule; ET, endothelin; ROS, Reactive oxygen species; ETA, endothelin A; TXA2, Thromboxane A2; NO, Nitric oxide; cGMP, Cyclic guanosine monophosphate; PGF2α, Prostaglandin F2alpha; PKC, protein kinase C; DAG, Diacylglycerol; IP3, Inositol trisphosphate; Hb, Hemoglobin; SA, subarachnoid; Met, Metabolic.

Figure 2. Step-by-step flow diagram of the study

Figure 3. Timeline of the study

Supplemental Digital Content (SDC) #. Medium. Title.

SDC, part 1, Text, References of the concept map

SDC, part 2, Text, Enrolment

SDC, part 3, Text, Criteria for the evaluation of vasospasm and disability

SDC, part 4, Text, Blinding

SDC, part 5, Text, Adverse events definition

SDC, part 6, Text, Serious adverse events

SDC, part 7, Text, Adverse Event (AE) Reporting

SDC, part 8, Text, References for supplementary text

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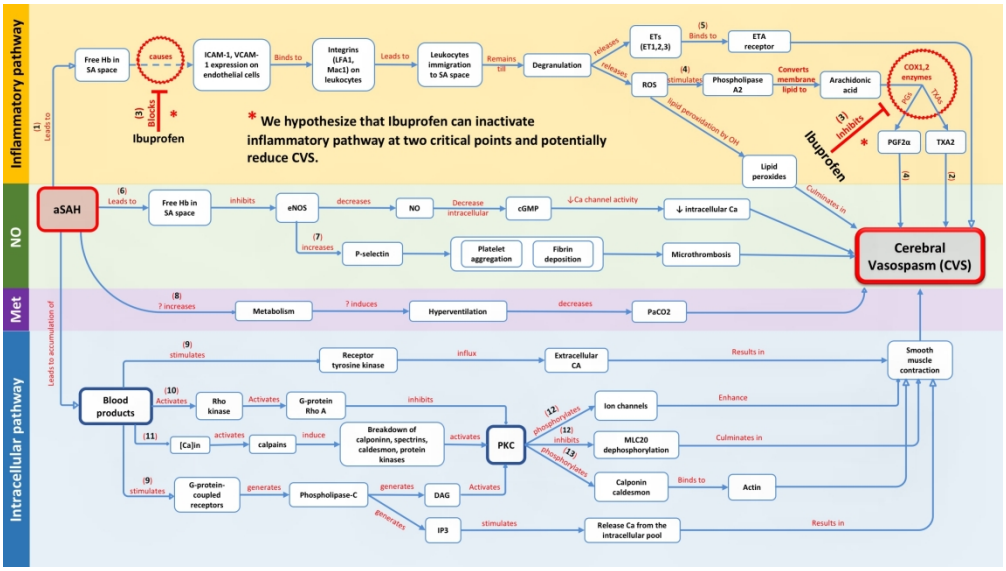

Figure 1. Concept map depicting four major pathways for the occurrence of cerebral vasospasm following aSAH. Inflammatory pathway is shown in yellow and explains how Ibuprofen may act as a prophylactic agent in this scenario. Numbers in parentheses are representative of corresponding reference for that branch, all concept map references are available in Supplemental digital content, part 1.
ICAM-1, Intercellular Adhesion Molecule 1; VCAM, vascular cell adhesion molecule; ET, endothelin; ROS, Reactive oxygen species; ETA, endothelin A; TXA2, Thromboxane A2; NO, Nitric oxide; cGMP, Cyclic guanosine monophosphate; PGF2, Prostaglandin F2alpha; PKC, protein kinase C; DAG, Diacylglycerol; IP3, Inositol trisphosphate; Hb, Hemoglobin; SA, subarachnoid; Met, Metabolic.

1057x595mm (72 x 72 DPI)

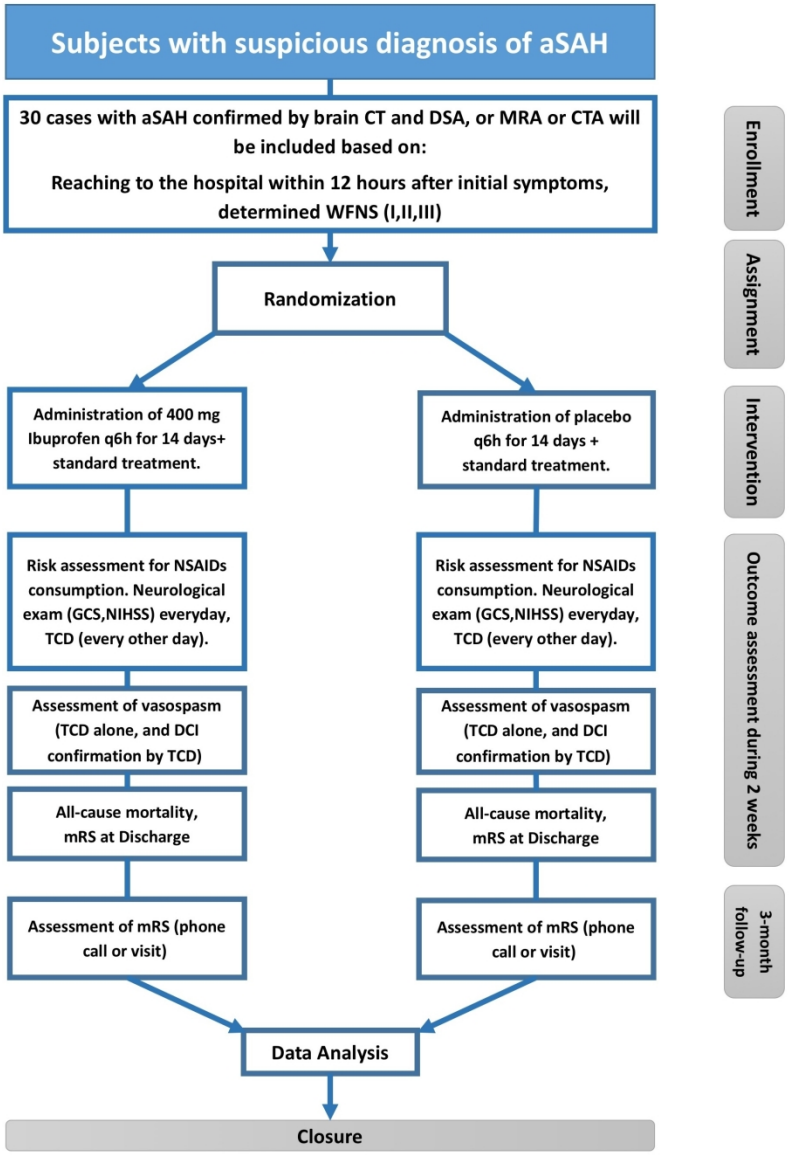

Figure 2. Step-by-step flow diagram of the study.

169x240mm (300 x 300 DPI)

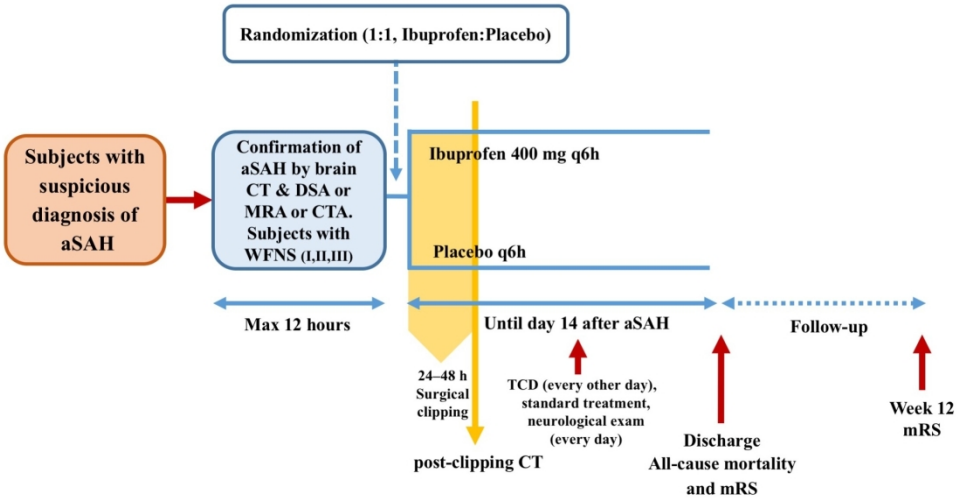

Figure 3. Timeline of the study

734x396mm (72 x 72 DPI)

Supplemental digital content (SDC)

Prophylactic effects of Ibuprofen on cerebral vasospasm following aneurysmal subarachnoid hemorrhage: Protocol for a randomised placebo-controlled pilot trial

Authors:

Mojtaba Dayyani[1, 2] Ermia Mousavi Mohammadi[2], Vahid Ashoorion[3], Behnam Sadeghirad[3], Mohammadreza javedani yekta[2], James Grotta[4], Nestor Gonzalez[5], Samira Zabihiyan[2, *]

Table of Contents

SDC, part 1. References of the concept map

1. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World Neurosurg.* 2010;73(1):22-41.
2. Viski S, Olah L. Use of Transcranial Doppler in Intensive Care Unit. *J Crit Care Med (Targu Mures).* 2017;3(3):99-104.
3. Nassiri F, Ibrahim GM, Badhiwala JH, et al. A Propensity Score-Matched Study of the Use of Non-steroidal Anti-inflammatory Agents Following Aneurysmal Subarachnoid Hemorrhage. *Neurocrit Care.* 2016;25(3):351-358.
4. Ibuprofen: Drug information. In: *UpToDate.*2017.
5. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. *New England Journal of Medicine.* 1991;324(24):1716-1725.
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-2035.
7. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology.* 2008;52(18):1502-1517.
8. Huerta C, Castellsague J, Varas-Lorenzo C, Rodríguez LAG. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *American Journal of Kidney Diseases.* 2005;45(3):531-539.
9. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA internal medicine.* 2014;174(11):1755-1762.
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14. Luciano R. NSAIDs: Acute kidney injury (acute renal failure). In: Palevsky PM, Sheridan A, eds. *UpToDate.*2017.
15. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *Journal of Allergy and Clinical Immunology.* 2007;119(4):1016.
16. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *Journal of Allergy and Clinical Immunology.* 2001;108(5):871-873.

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18. Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. *Current opinion in allergy and clinical immunology.* 2010;10(4):354-361.

SDC, part 2. Enrolment

Patient screening for eligibility and recruitment will be conducted at Ghaem Teaching Hospital, Mashhad, Iran. Two neurosurgery residents will first visit the patients and check the eligibility criteria in the emergency department. The neurosurgical intensive care unit of our center annually receives 100–150 patients with aSAH. Over twelve months, 30 eligible patients will be enrolled in our trial.

The recruited patient who met the criteria will sign and date the institutional informed consent form of the Mashhad University of Medical Sciences before allocating to each group and before initiation of any procedures related to the clinical investigation are performed. Then, required data will be gathered in specific datasheets, including demographic data (name, age, gender, address, and phone number), past medical history including cardiovascular, kidney, and liver diseases, previous episode of SAH, drug history including long term and recent use of any NSAIDs, anti-platelet medications and sensitivity to aspirin or any NSAIDs. Two nurses of the hospital's intensive care unit will fill case report forms (CRFs) and gather these data. In the absence of exclusion criteria, a file will be specified to each patient that contains a registration form, consent form, diagnostic form, and a 3-months follow-up evaluation sheet.

CRFs will be kept in a file that assigns to each patient. The research coordinator enters data from forms to a data management tool. Only the research coordinator has access to data in a password-protected spreadsheet till the study will be terminated. After this period, the research coordinator will send the spreadsheet to the method center located in the hospital. Also, to assess the patients' disability, a 3-months follow-up will be accomplished via a phone call or a clinic visit by two independent neurosurgery residents.

Participants who are unable to complete the protocol due to death, clinical complication, or being discharged for any reason will not be excluded from the study. The statisticians will apply the intention to treat analysis.

SDC, part 3. Criteria for the evaluation of vasospasm and disability

Chronic vasospasm can occur clinically with signs and symptoms or non-clinically that would be diagnosed by imaging [1]. In this study, we defined clinical vasospasm as delayed cerebral ischemia (DCI) and diagnosed non-clinically by Transcranial Doppler (TCD). 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 tomography,[2,3] or increases at least two scores of the National Institutes of Health Stroke Scale (NIHSS) [4]; in this condition, vasospasm will be confirmed by TCD.

The flow velocity of the middle cerebral artery (MCA) and the basilar artery is measured by TCD at the admission, then every two days. The timeline of the interventions is depicted in figure 3. In MCA, the flow velocity between 120-149 cm/s and Lindegaard ratio 3 to 6 was considered as mild vasospasm (25% vessel obstruction), velocity between 150-199 cm/s and Lindegaard ratio 3 to 6 as moderate vasospasm (50% obstruction) and a velocity more than or equal to 200 cm/s and a Lindegaard ratio greater than 6 as severe vasospasm (more than 50% occlusion). In the basilar artery, the flow velocity between 70-85 cm/s and Lindegaard ratio 2 to 2.49 was considered as mild vasospasm (25% vessel obstruction), the velocity greater than 85 cm/s, and Lindegaard ratio between 2.5 to 2.99 as moderate vasospasm (50% obstruction) and a velocity over 85 cm/s and the Lindegaard ratio greater than or equal to 3 as severe vasospasm (more than 50% obstruction) [5].

Disability will be assessed at discharge and three months after discharge based on the Modified Rankin Scale (mRS). Favorable mRS outcomes are (mRS 1 and 2), and unfavorable outcomes are (mRS 3 to 6).

SDC, part 4. Blinding

Participants of both groups will be blinded to take their correspondent medication or placebo. Also, ibuprofen and placebo will be packed in identical capsules, and they are not distinguishable by participants or study personnel.

The clinical team, including neurosurgeons, radiologists and, ICU department staff, and the neurologist who does TCD, are not aware of which group patients belong to. Outcomes will be recorded in a list based on patient allocation to either group A or B. Likewise, the statistician would

not be aware of what data belongs to either the intervention or placebo groups in the final datasheet. Breaking of the treatment codes will be carried out three months after the inclusion of the last eligible patient. All outcome assessments will be performed before the treatment codes are broken.

SDC, part 5. Adverse events definition

Oral administration of ibuprofen has some common adverse reactions that their prevalence is ranged between 1-10%. In these conditions, it is not necessary to discontinue drug consumption. Edema due to fluid retention occurs in 1 to 3%. Central nervous system reactions included dizziness (3-9%), headache (1-3%), and nervousness (1-3%). Skin rashes (3-9%) and pruritus (1-3%) are dermatologic reactions that may occur by ibuprofen consumption. There are some adverse events in the gastrointestinal system which may arise from ibuprofen, including epigastric pain (3-9%), heartburn (3-9%), nausea (3-9%), abdominal pain (1-3%), constipation (1-3%), decreased appetite (1-3%), diarrhea (1-3%), dyspepsia (1-3%), vomiting (1-3%). Tinnitus is the otic complications which may happen by the prevalence of 3-9% [6].

SDC, part 6. Serious adverse events

The first possible serious adverse events are cardiovascular thrombotic events, including myocardial infarction (MI). Another serious cardiovascular event is new-onset hypertension or exacerbation of hypertension [7]. We will strictly monitor blood pressure as a part of our routine management in the ICU, which helps us detect this event before its remarkable increment.

In general, using the lowest effective dose for the shortest duration of time might reduce the risk of cardiovascular events. In our study, these conditions are considered. In case of any clinical suspicion for MI, in the initial assessment phase, a 12-lead ECG, an abbreviated history, and physical examination will obtain within 10 minutes [8]. Then, the serum level of Troponin-I will be measured, and cardiology consultation will be requested for further evaluation or possible therapeutic interventions.

Gastrointestinal events, including an increased risk of ulceration, bleeding, and perforation, are the second possible serious adverse events. Elderly patients and patients with a history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [9]. We avoid enrolling

patients with a history of acute GI bleeding. Concomitant gastro-protective therapy (e.g., proton pump inhibitors (PPIs) [10] is recommended; as mentioned in the safety section, we use PPIs for all study participants. For the initial evaluation of the patient with the signs of active upper GI bleeding, hemodynamic stability, and the necessity for fluid resuscitation will be assessed. Intravenous pantoprazole at the dose of 40 mg twice daily will be initiated for these patients [11]. Endoscopy within 24 hours of presentation for the diagnosis and treatment of active upper GI bleeding will be accomplished [12].

The third serious adverse event secondary to ibuprofen use is the accentuation of existing renal dysfunction that is dose-dependent [10]. The proposed criteria for acute kidney injury[13] include an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or an increase to ≥1.5 times the presumed baseline value that is known to have occurred within the last seven days or a decrease in urine volume to <3 mL/kg over six hours [14]. The diagnosis of hemodynamically mediated AKI associated with NSAIDs is suggested by recent NSAID use, the absence of significant proteinuria (<500 mg/day), hematuria, and the bland urine sediment. Among patients with AKI, generally, a renal ultrasound will be done to exclude possible obstruction. In general, the diagnosis is made when kidney function recovery occurs after the NSAID is discontinued [15]. For the treatment of NSAID-induced AKI, the NSAID should be stopped immediately, volume resuscitation will be provided in states of hypovolemia and continued based on a reassessment of volume status including blood pressure/pulse and urine output [16].

The fourth serious adverse event is anaphylactic reactions. The most common signs and symptoms are cutaneous (e.g. sudden onset of generalized urticarial, angioedema, flushing, and pruritus). Airway will be assessed at first [17]. Epinephrine will be given 0.3 to 0.5 mg intramuscularly (IM), which can be repeated every 5 to 15 minutes. Oxygen will be given 8-10 L/min via face mask as needed. Hypotension, if occurs, will be managed via rapid infusion of 1 to 2 liters intravenously. Adjunctive therapies including IV diphenhydramine 25 to 50 mg, IV ranitidine 50 mg, IV methylprednisolone 125 mg, and monitoring hemodynamic, pulse oximetry, and urine output will be considered as appropriate [18-20].

Unanticipated problems resulting in risk to participant or others

Any incident, experience, or outcome that meets the following criteria:

- Unexpected in nature, severity, or frequency (e.g., not described in study-related documents such as the ethics-approved protocol or consent form, etc.).
- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience or outcome may have been caused by the procedures involved in the research), and suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm)

SDC, part 7. Adverse Event (AE) Reporting

The clinical site (ICU nurse and neurosurgery resident) is responsible for reporting AEs to the Methods Centre promptly. Significant new information on ongoing AEs should also be provided promptly to the Methods Centre via the data capture system. Unanticipated problems resulting in risk to participants or others are also to be reported promptly to the Methods Centre.

The clinical site is responsible for reporting AEs and unanticipated problems resulting in risk to participants or others to their local ethics committee in accordance with local reporting requirements. Copies of each report and documentation of ethic board notification and receipt will be kept in the clinical site's study file. The Methods Centre will be responsible for reporting any applicable adverse events to the relevant regulatory bodies (e.g., Food and Drug organization, adverse events registration).

SDC, part 8. References for supplementary text

1. Chaichana KL, Pradilla G, Huang J, Tamargo RJ. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World Neurosurg.* 2010;73(1):22-41.
2. Vergouwen MD, Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid H. Vasospasm versus delayed cerebral ischemia as an outcome event in clinical trials and observational studies. *Neurocrit Care.* 2011;15(2):308-311.
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4. Nassiri F, Ibrahim GM, Badhiwala JH, et al. A Propensity Score-Matched Study of the Use of Non-steroidal Anti-inflammatory Agents Following Aneurysmal Subarachnoid Hemorrhage. *Neurocrit Care.* 2016;25(3):351-358.
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8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-2035.
9. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology.* 2008;52(18):1502-1517.
10. Huerta C, Castellsague J, Varas-Lorenzo C, Rodríguez LAG. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *American Journal of Kidney Diseases.* 2005;45(3):531-539.
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13. Shiba M, Suzuki H, Fujimoto M, et al. Role of platelet-derived growth factor in cerebral vasospasm after subarachnoid hemorrhage in rats. *Acta Neurochir Suppl.* 2013;115:219-223.
14. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of the American Society of Nephrology.* 2005;16(11):3365-3370.
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20. Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. *Current opinion in allergy and clinical immunology.* 2010;10(4):354-361.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No in the manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page and 17
	5b	Name and contact information for the trial sponsor	Title page
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 14, 15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5, 6
	6b	Explanation for choice of comparators	6, 9

Objectives	7	Specific objectives or hypotheses	7, 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13 and supplement 4,5, and 6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12, 14, 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9, 13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2, 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12, 14, 15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10 and supplement 3
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10 and supplement 3
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10 and supplement 3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7 and supplement 3
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11, 12

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 12, 13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11, 12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11, 12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11, 12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14, 15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13, 14 and supplement 4,5, and 6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14, 15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Title page
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11,12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Via Publication
	31b	Authorship eligibility guidelines and any intended use of professional writers	ICMJE
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available in Farsi
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.