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Preventive effect of ibuprofen on the spasms of brain arteries following brain hemorrhage

Submission date
05/06/2020

Recruitment status
No longer recruiting

Registration date
19/08/2020

Overall study status
Completed

Last Edited
06/09/2023

Condition category
Circulatory System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
When brain arteries bleed abruptly into the subarachnoid space (the interval between the arachnoid membrane and the pia mater, containing cerebrospinal fluid), a subarachnoid hemorrhage has occurred. The most common cause of subarachnoid hemorrhage is the bulging of a cerebral artery wall called an aneurysm.
One of the serious complications of subarachnoid hemorrhage is the transient narrowing of the arteries (due to spasms) which is called cerebral vasospasm. Cerebral vasospasm is the main cause of mortality and morbidity following an aneurysmal subarachnoid hemorrhage. As the cerebral arteries provide glucose and oxygen for brain tissue, a reduced blood supply causes cerebral ischemia in about more than two-thirds of patients who experience aneurysmal subarachnoid hemorrhage. Also, a considerable portion of the survivors suffers neurological symptoms like paralysis, numbness, and etc.
The exact mechanisms of the cerebral vasospasm are not well understood. However, there are some pieces of evidence that demonstrate the important role of inflammation. The aim of this study is to investigate whether anti-inflammatory medications can prevent cerebral vasospasm. Evaluation of the vascular spasms will be implemented by the doppler sonography of cerebral arteries.

Who can participate?
Patients with subarachnoid hemorrhage following the rupture of a cerebral aneurysm can participate in this study.

What does the study involve?
Patients are randomly allocated into two groups. The first group will take ibuprofen and for the second group, a sham will be administered that is totally similar to the drug. Participants in both groups will take either the drug or sham for two weeks, four times a day, and both groups will receive standard treatment at the same time.

What are the possible benefits and risks of participating?
Although evidence from some in vitro and very limited human experiments are promising for the possible preventive effects of ibuprofen on cerebral vasospasm, we might not see those benefits among participants. However, it is a worthwhile opportunity to support a research that

directly helps to discover possible new pathways in the prevention of cerebral vasospasm and its mishaps secondary to the complications.
Ibuprofen is a commonly used non-steroidal anti-inflammatory drug (NSAID) that may have some adverse effects such as dizziness, heartburn, nausea, rash, and tinnitus in people without comorbidities. Acute kidney injury is a rare adverse effect of these medications. The most serious adverse effects of NSAIDs are gastrointestinal (GI) bleeding and increased risk of some heart diseases. Nonetheless, the administration of anti-acid medications can significantly lower the occurrence of GI complications. Also, previous long term consumption of antiplatelet medications like aspirin is a predisposing factor for GI bleeding. Patients with existing heart disease or risk factors for such diseases may be at greater risk for heart complications. In this study, before enrollment, patients will be assessed for risk factors and will be stratified based on their chronic diseases and type of their medications to exclude those with high risk and decrease the probability of any mishap for the others as much as possible. Also, the participants are under 24-hour close observation of our clinical experts in the intensive care unit and any possible complications will be managed promptly by them based on the institutional protocols.

Where is the study run from?
The study will be conducted in Qaem teaching Hospital (Mashhad, Iran).

When is the study starting and how long is it expected to run for?
September 2018 to July 2022

Who is funding the study?
Mashhad University of Medical Sciences (MUMS).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
971587

Study information

Scientific Title
Prophylactic effects of ibuprofen vs placebo on cerebral vasospasm following aneurysmal subarachnoid hemorrhage: a single-center randomized, controlled pilot trial

Study objectives
Ibuprofen can prevent subsequent cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/04/2019, Mashhad University of Medical Sciences (MUMS) ethical committee (Mashhad University of Medical Sciences, Ghorashi building, Daneshgah Street, Mashhad, 91388-13944, Iran; +98 5138411538; vcresearch@mums.ac.ir), ref: IR.MUMS.MEDICAL.REC.1398.225

Study design
Single-center feasibility study for a double-blind randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Vasospasms following aneurysmal subarachnoid hemorrhage

Interventions
Eligible participants are adult patients 18 years old and older with an aneurysmal subarachnoid hemorrhage confirmed by a brain CT scan, CT angiography, magnetic resonance angiography or digital subtraction angiography who admitted to the emergency department within 6 hours of the ictus. Those who meet the inclusion criteria will be randomized based on a generated permuted block randomization table using an online random sequence generator with an allocation list in random order. The allocation ratio is 1:1. Then, an independent investigator allocates participants into two groups for the administration of either ibuprofen or placebo. The intervention group will receive Ibuprofen capsules 400 mg/every 6 hours for 14 days. Placebo is given to the control group. At the same time, both groups will concomitantly be treated by the standard of care of aSAH treatment for 2 weeks including nimodipine and phenytoin. Microsurgical aneurysmal clipping or interventional coiling will be performed for patients who have an indication based on the researchers' protocols.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ibuprofen

Primary outcome measure
Feasibility outcomes (measured using case report forms):
1. Ability to recruit 30 participants over 12 months
2. Ability to follow 85% of participants for 3 months
3. Patient compliance with the study treatment if 75% of participants comply with 75% of the protocol

Secondary outcome measures
Outcomes for the definitive trial:
1. All-cause mortality until discharge and by the end of follow-up measured using patient records
2. Cerebral vasospasm: defined as detection of vasospasm by either digital subtraction angiography (DSA) or transcranial Doppler (TCD). Angiographic vasospasm is defined as focal or generalized reduction of cerebral arterial caliber on conventional cerebral angiogram. TCD vasospasm is defined as any peak systolic middle cerebral artery velocity (PSVMCA) _120 cm/s and a Lindegaard ratio of >3 and it will be assessed every other day during the hospitalization
3. Delayed cerebral ischemia (DCI): The occurrence of DCI defined as the development of new, focal neurological deficits, and/or a decreased level of consciousness of at least two points on the Glasgow Coma Scale (GCS) after other possible causes of deterioration have been excluded assessed every other day during the hospitalization
4. Disability at discharge and 3 months using Modified Rankin Scale (mRS) at three-month follow-up. Favorable mRS outcomes are (mRS 1 and 2) and unfavorable outcomes are (mRS 3 to 6)

Overall study start date
08/09/2018

Completion date
29/07/2022

Eligibility

Key inclusion criteria
1. Aneurysmal subarachnoid hemorrhage verified by a brain CT scan
2. Older than 18 years old
3. Admitted less than 6 hours after the onset of clinical symptoms
4. World Federation of Neurological Surgeons (WFNS) score I, II and III at admission

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
There are 30 participants in this study

Key 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, and pregnancy
4. Patients with a history of myocardial infarction(MI) or percutaneous coronary interventions

Date of first enrolment
01/06/2020

Date of final enrolment
29/04/2022

Locations

Countries of recruitment
Iran

Study participating centre
Ghaem teaching Hospital
Ahmad Abad Blvd
Mashhad
Iran
99199-91766

Sponsor information

Organisation
Mashhad University of Medical Sciences

Sponsor details
Knowledge and Health City
Shahid Fakouri Blvd (In front of Fakouri 94)
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91778-99191
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Sponsor type
University/education

Website
http://www.mums.ac.ir/

ROR
https://ror.org/04sfka033

Funder(s)

Funder type
University/education

Funder Name
Mashhad University of Medical Sciences

Alternative Name(s)
MUMS

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Iran

Results and Publications

Publication and dissemination plan

Due to the Covid-19 pandemic, all medical resources and hospital beds dedicated to these patients during each peak, it is anticipated that the results of this study will be presented by mid 2022 and the article will be published during late 2022
(updated 13/07/2021, previously: It is anticipated that the results of this study will be presented in international meetings, early 2021 and the article will be published during late 2021.)

Intention to publish date

31/12/2022

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		12/04/2022	06/09/2023	Yes	No