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, *]

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SDC, part 1. References of the concept map

1. Chaichana KL, Pradilla G, Huang J, et al. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World neurosurgery* 2010;73(1):22-41. doi: 10.1016/j.surneu.2009.05.027 [published Online First: 2010/05/11]
2. van den Bergh WM, Algra A, Dorhout Mees SM, et al. Randomized controlled trial of acetylsalicylic acid in aneurysmal subarachnoid hemorrhage: the MASH Study. *Stroke* 2006;37(9):2326-30. doi: 10.1161/01.STR.0000236841.16055.0f [published Online First: 2006/08/05]
3. Frazier JL, Pradilla G, Wang PP, et al. Inhibition of cerebral vasospasm by intracranial delivery of ibuprofen from a controlled-release polymer in a rabbit model of subarachnoid hemorrhage. *Journal of neurosurgery* 2004;101(1):93-8. doi: 10.3171/jns.2004.101.1.0093 [published Online First: 2004/07/17]
4. Chyatte D. Prevention of chronic cerebral vasospasm in dogs with ibuprofen and high-dose methylprednisolone. *Stroke* 1989;20(8):1021-26.
5. Kobayashi H, Hayashi M, Kobayashi S, et al. Cerebral vasospasm and vasoconstriction caused by endothelin. *Neurosurgery* 1991;28(5):673-79.
6. Edwards DH, Byrne JV, Griffith TM. The effect of chronic subarachnoid hemorrhage on basal endothelium-derived relaxing factor activity in intrathecal cerebral arteries. *Journal of neurosurgery* 1992;76(5):830-37.
7. Sabri M, Ai J, Lakovic K, et al. Mechanisms of microthrombi formation after experimental subarachnoid hemorrhage. *Neuroscience* 2012;224:26-37.
8. Westermaier T, Stetter C, Kunze E, et al. Controlled hypercapnia enhances cerebral blood flow and brain tissue oxygenation after aneurysmal subarachnoid hemorrhage: results of a phase 1 study. *Neurocritical care* 2016;25(2):205-14.
9. Tani E. Molecular mechanisms involved in development of cerebral vasospasm. *Neurosurgical focus* 2002;12(3):1-8.
10. Chrissobolis S, Sobey CG. Recent evidence for an involvement of rho-kinase in cerebral vascular disease. *Stroke* 2006;37(8):2174-80.
11. Macdonald R. Pathophysiology and molecular genetics of vasospasm. Cerebral Vasospasm: Springer 2001:7-11.
12. Laher I, Zhang JH. Protein kinase C and cerebral vasospasm. *Journal of Cerebral Blood Flow & Metabolism* 2001;21(8):887-906.
13. Kolias AG, Sen J, Belli A. Pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: putative mechanisms and novel approaches. *Journal of neuroscience research* 2009;87(1):1-11.

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.

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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, et al. Role of inflammation (leukocyte-endothelial cell interactions) in vasospasm after subarachnoid hemorrhage. *World Neurosurg* 2010;73(1):22-41. doi: 10.1016/j.surneu.2009.05.027 [published Online First: 2010/05/11]
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):308-11. doi: 10.1007/s12028-011-9586-8
3. Vergouwen MDI, Vermeulen M, Gijn Jv, et al. Definition of Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage as an Outcome Event in Clinical Trials and Observational Studies. *Stroke* 2010;41(10):2391-95. doi: doi:10.1161/STROKEAHA.110.589275
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):351-58. doi: 10.1007/s12028-016-0266-6 [published Online First: 2016/03/24]
5. Viski S, Olah L. Use of Transcranial Doppler in Intensive Care Unit. *J Crit Care Med (Targu Mures)* 2017;3(3):99-104. doi: 10.1515/jccm-2017-0021 [published Online First: 2018/07/04]
6. Ibuprofen: Drug information. UpToDate2017.
7. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. *New England Journal of Medicine* 1991;324(24):1716-25.
8. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126(16):2020-35.
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):1502-17.
10. Huerta C, Castellsague J, Varas-Lorenzo C, et al. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *American Journal of Kidney Diseases* 2005;45(3):531-39.
11. 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):1755-62.
12. Marmo R, Rotondano G, Piscopo R, et al. 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.
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;115:219-23. doi: 10.1007/978-3-7091-1192-5_40 [published Online First: 2012/08/15]
14. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of the American Society of Nephrology* 2005;16(11):3365-70.
15. Whelton A, Stout RL, Spilman PS, et al. 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):568-76.
16. Luciano R. NSAIDs: Acute kidney injury (acute renal failure). In: Palevsky PM, Sheridan A, eds. UpToDate2017.
17. 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.
18. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular versus subcutaneous injection. *Journal of Allergy and Clinical Immunology* 2001;108(5):871-73.
19. Pumphrey RS. Fatal posture in anaphylactic shock. *Journal of Allergy and Clinical Immunology* 2003;112(2):451-52.
20. Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. *Current opinion in allergy and clinical immunology* 2010;10(4):354-61.