neurocritical care society Neurocrit Care (2016) 25:351–358
DOI 10.1007/s12028-016-0266-6

ORIGINAL ARTICLE

A Propensity Score-Matched Study of the Use of Non-steroidal Anti-inflammatory Agents Following Aneurysmal Subarachnoid Hemorrhage

Farshad Nassiri[1,2,3,4] · George M. Ibrahim[1,2,3,4] · Jetan H. Badhiwala[1,2,3,4] · Christopher D. Witiw[1,2,3,4] · Alireza Mansouri[1,2,3,4] · Naif M. Alotaibi[1,2,3,4] · R. Loch Macdonald[1,2,3,4]

Published online: 21 March 2016

Abstract

Background Inflammation may contribute to poor outcomes after aneurysmal subarachnoid hemorrhage (aSAH). Here, we compared outcomes among propensity score-matched cohorts who did and did not receive non-steroidal anti-inflammatory drug (NSAID) use after aSAH.

Methods Propensity score-matched analysis of 413 subjects enrolled in the Clazosentan to Overcome Neurological iSChemia and Infarction OccUring after Subarachnoid hemorrhage (CONSCIOUS-1) study. Propensity score matching was performed on the basis of age, sex, baseline National Institutes of Health Stroke Scale score, World Federation of Neurological Societies grade on admission, procedure used for securing aneurysm, and SAH clot burden.

Results 178 patients were matched (89 received NSAIDs, 89 did not). Propensity score matching was considered acceptable. Patients who had received NSAIDs during their hospital stay had significantly lower mortality rate, and reduced duration of intensive care unit stay and total length of hospital stay ($P = 0.035$, $P = 0.009$, and $P = 0.053$, respectively). At 6 weeks, 80.9 % of patients treated with NSAIDs had good functional outcome compared to 68.5 % of matched controls ($P = 0.083$). There was no significant difference in the proportions of patients who developed delayed ischemic neurological deficits, angiographic vasospasm, or required rescue therapy.

Conclusions Inflammation may play a crucial role in the poor outcomes after SAH, and that NSAIDs may be a useful therapeutic option, once validated by larger prospective studies.

Keywords Aneurysm · Critical care · NSAID · Subarachnoid hemorrhage · Intensive care

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 5–10 % of all strokes worldwide, culminating in a total of 600,000 new cases per year [1]. Despite significant advances in treatments, there continues to be high case-fatality and morbidity rates, as well as disproportionately high resource utilization, including prolonged intensive care unit (ICU) stays [2]. Patients who survive the initial insult remain at risk of neurological deterioration as a consequence of the aneurysm-securing procedure, angiographic vasospasm and delayed cerebral ischemia (DCI), as well as medical interventions instigated during the hospital stay [3].

Increasingly greater impetus has been placed on the identification of novel therapeutics that may mitigate neurological insult following aSAH. Several drugs, including magnesium, tirilazad, and clazosentan, have been the focus of recent trials, and although these drugs showed promising results in early clinical studies, large randomized

Clinical Trial Registration: URL - www.clinicaltrials.gov; Unique Identifier - NCT00111085.

✉ R. Loch Macdonald
MacdonaldLo@smh.ca

[1] Division of Neurosurgery, St. Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1W8, Canada

[2] Labatt Family Centre of Excellence in Brain Injury and Trauma Research, St. Michael's Hospital, Toronto, Canada

[3] Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada

[4] Department of Surgery, University of Toronto, Toronto, ON, Canada

trials found no clinical benefit [4–6]. To date, nimodipine remains the only drug approved for use in SAH, as it has proven to reduce the risk of DCI and poor outcome [7].

While the cause of poor outcomes after SAH is multifactorial, several studies support the notion that they may be mediated by local and systemic inflammatory responses. Inflammatory markers, such as neutrophils, TNF-α, and various interleukins, are up-regulated in plasma and cerebrospinal fluid (CSF) after SAH, and these are correlated with poor neurological outcome [8–10]. Moreover, the systemic inflammatory response syndrome (SIRS) is associated with poor outcomes after SAH and is present in up to 63 % of patients after SAH [11, 12]. This has spurred interest in the use of anti-inflammatory drugs after SAH. Non-steroidal anti-inflammatory drugs (NSAIDs), which are commonly administered to patients in the ICU, are unique in that they provide anti-pyretic and analgesic effects, in addition to their anti-inflammatory properties. Their clinical utility following SAH remains controversial, as the few experimental and clinical studies on the topic have shown mixed results.

In the present study, we sought to investigate whether NSAID use was associated with improved outcomes after aneurysmal SAH. We performed an exploratory analysis using propensity score matching of subjects enrolled in the Clazosentan to Overcome Neurological iSChemia and Infarction OccUring after Subarachnoid hemorrhage (CONSCIOUS-1) study. This "pseudorandomization" methodology has the advantage of directly evaluating the effects of the drug administered while accounting for confounding factors.

Methods

Study Participants

We performed a post hoc analysis of 413 subjects enrolled in the CONSCIOUS-1 study. This was a multicentre, randomized, double-blinded, placebo-controlled, phase IIb dose-finding, efficacy, and safety trial of clazosentan in aneurysmal SAH [13].

Assessments and Outcomes

Eligible patients had aneurysmal SAH confirmed by digital subtract angiography (DSA), and presented with World Federation of Neurosurgical Societies (WFNS) grades I to IV on admission or were grade V on admission and improved to grade IV or less after resuscitation and ventriculostomy [14]. Patients were admitted to the respective neurosurgical units of participating centers. Medical management of patients was at the discretion of the treating physicians according to standard of care, including oral or intravenous nimodipine. Aneurysm securing by clipping or coiling was performed after baseline DSA.

All medication administration was recorded daily for 14 days after aneurysmal rupture. Patients who were noted to have been receiving NSAIDs, including salicylates (aspirin), propionic acid derivatives (ibuprofen, naproxen), acetic acid derivatives (indomethacin, ketorolac, diclofenac), enolic acid derivatives (meloxicam), and selective cyclooxygenase-2 inhibitors (-coxib's), during this time period, were identified.

Repeat DSA was performed routinely at 7–11 days post aneurysmal rupture and additionally as clinically indicated. Angiographic vasospasm was defined as the change in diameter of large proximal vessels on DSA when comparing baseline to subsequent imaging. The severity of vasospasm was quantified as the degree of change in vessel diameter.

CT was also performed within 48 h of admission, 48 h after aneurysm securing, and at 6 weeks after aneurysmal rupture. To mitigate any inter-reader bias, all imaging was reviewed centrally by 2 independent, blinded reviewers. Baseline CT was assessed for SAH clot burden (Hijdra scale [15]) and intraventricular hemorrhage (Graeb scale [16]) as well as other acute intracranial abnormalities. On 6-week CT, the presence and volume of infarcts were measured and compared to the post-procedural CT. Any infarcts present on the 6 week scan and not present on the post-procedural scan were considered as delayed cerebral infarcts (DCI).

Clinical outcomes included 6-week mortality, 12-week modified Rankin scale (mRS) score, DCI, and delayed ischemic neurological deficit (DIND). DIND was defined as any angiographic vasospasm (as determined by DSA or transcranial Doppler ultrasound) that was associated with neurological deterioration lasting for a minimum of 2 h without any other cause identified. Neurological deterioration was defined as a drop of more than 1 point on the Glasgow Coma Scale (GCS) or an increase in at least two points on the National Institutes of Health Stroke Scale (NIHSS). In circumstances when a neurological exam was not possible, or when a new hypodensity was observed on CT, DIND was defined as clinical signs with angiographic evidence of vasospasm.

Propensity Score-Matching and Statistical Analyses

As patients were not randomized to receive NSAIDs, propensity score matching was performed with exposure to NSAID administration at any point during treatment as the dichotomous treatment group. The following covariates were balanced between the two cohorts: age, sex, baseline NIHSS score, WFNS grade on admission, procedure used

for securing aneurysm, and SAH clot burden. Matching was performed using calipers of width equal to 0.25 times the standard deviation of the logit of the propensity scores with a 1:1 ratio between treatment group and controls. While previous work has shown this to be the optimal caliper width for propensity matching [17], we also assessed covariate balance between the two groups for each pre-treatment variable by plotting propensity score distribution histograms. All statistical analyses were performed using R statistical software. Continuous variables were compared using a two-tailed t test and proportions were compared using the Fisher exact test, unless otherwise specified. A P value of <0.05 was considered to be statistically significant.

Results

Patient Demographics

Of the 413 patients enrolled in the CONSCIOUS-1 trial, 95 received NSAIDs. After excluding patients with missing information, 89 patients who received NSAIDs during their hospital stay were matched to an equal number of patients who did not take NSAIDs using a propensity scoring algorithm. The distributions of the propensity scores were acceptable (Fig. 1). The mean age of the propensity-matched cohort was 50.6 ± 10.2 years. The majority of subjects (71.9 %) were female. There were no significant differences in baseline clinical and radiographic features of propensity score-matched groups, including baseline inflammatory status (Table 1).

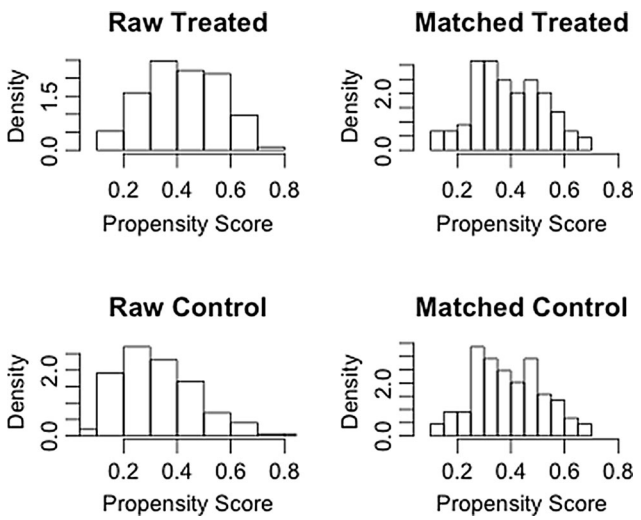

Fig. 1 Density histograms of treatment and control groups before and after propensity score matching. Propensity score distributions are more similar between treatment and control groups after matching

Clinical Outcomes

The 6-week mortality rate was significantly lower in patients who had received NSAIDs during their hospital stay compared to matched controls (Table 2; OR 8.61, 95 % CI 1.11–389.22, $P = 0.035$). At 6 weeks, 80.9 % of patients treated with NSAIDs had good functional outcome (mRS score <2) compared to 68.5 % of matched controls (Table 2; OR 1.93, 95 % CI 0.92–4.15, $P = 0.083$). There was no significant difference in the proportions of patients who developed DIND (14.9 vs. 20.2 %, $P = 0.420$), DCI (23.6 vs. 29.2 %, $P = 0.496$), angiographic vasospasm (41.6 vs. 44.9 %, $P = 0.762$), or required rescue therapy (20.2 vs. 20.2 %, $P = 1.00$).

Complications

Complications specific to the use of NSAIDs were not directly recorded within the trial database. We therefore compared total duration of hospital stay, duration of ICU stay, and duration of ward stay between the two cohorts. Patients treated with NSAIDs had significantly reduced duration of ICU stay (Table 2; 23.6 vs. 30.8 days, $P = 0.009$) and reduced total length of stay (Table 2; 45.1 vs. 52.6 days, $P = 0.053$).

Discussion

This exploratory analysis suggests that NSAID use after aneurysmal SAH may be associated with improved outcome, a finding that appears to be independent of angiographic vasospasm, DINDs, or DCI. Moreover, our analysis found that patients receiving NSAIDs may have shorter ICU and hospital stays. Our findings support the hypothesis that inflammation after aneurysmal SAH may contribute to poor outcomes. Although patients in the database were not randomized to receive NSAIDs, we are able to infer that the use of NSAIDs may improve outcomes after aneurysmal SAH by applying a propensity score-matching analysis.

Early reports supporting a role for inflammation in the pathogenesis of SAH found that non-infectious causes of fever and leukocytosis were significantly higher in patients with ruptured aneurysms [18, 19], although the extent to which inflammation mediated endogenous repair as opposed to brain injury was unclear. It has been since established that erythrocyte extravasation into the subarachnoid space following aneurysmal rupture may lead to the deposition of toxic-free hemoglobin [20]. Endothelial cells at the site of rupture also express specific cell adhesion molecules, such as p-selectin, that allow for attachment of the endothelial cells to specific integrin

Table 1 Baseline clinical and radiographic characteristics by treatment group

	NSAID ($N = 89$)	Control ($N = 89$)	P value
Age	50.6 ± 9.8	50.7 ± 11.1	0.932
Sex (male)	26 (29.2 %)	23 (25.8 %)	0.737
WFNS grade			0.914
I	38 (42.7 %)	41 (46.1 %)	
II	30 (33.7 %)	27 (30.3 %)	
III	1 (1.1 %)	2 (2.2 %)	
IV	19 (21.3 %)	19 (21.3 %)	
V	1 (1.1 %)	0	
Clazosentan treatment			0.7102
Placebo	22 (24.7 %)	20 (22.5 %)	
1 mg/h	21 (23.6 %)	17 (19.1 %)	
5 mg/h	24 (26.9 %)	31 (34.8 %)	
15 mg/h	22 (24.7 %)	21 (23.6 %)	
Procedure			0.313
Both	2 (2.2 %)	0	
Clipping	38 (42.7 %)	44 (49.4 %)	
Coiling	49 (55.1 %)	45 (50.6 %)	
Aneurysm location			0.628
Unspecified	3 (3.4 %)	3 (3.4 %)	
ACA	42 (47.2 %)2	39 (43.8 %)	
ICA/carotid terminus	24 (27.0 %)	33 (37.1 %)	
MCA	13 (14.6 %)	9 (10.1 %)	
Posterior circulation	7 (7.9 %)	5 (5.6 %)	
Subarachnoid clot burden (Hijdra score)	18.5 ± 4.8	19.0 ± 5.4	0.485
Inflammatory status			
Temperature >38 °C or < 36 °C	25 (31 %)	25 (36 %)	0.49
RR >20	10 (15 %)	9 (13 %)	0.81
HR >90	8 (9 %)	13 (15 %)	0.25
WBC >12 or <4	43 (53 %)	53 (70 %)	0.02
SIRS (>2 of the above)	19 (32 %)	19 (35 %)	0.84

Data are presented as N (%), mean ± SD, unless otherwise specified

ACA anterior cerebral artery, *HR* heart rate, *ICA* internal carotid artery, *MCA* middle cerebral artery, *RR* respiratory rate, *SIRS* systemic inflammatory response syndrome, *WBC* white blood cell, *WFNS* World Federation of Neurosurgical Societies

proteins on immune cells [21, 22]. This interaction facilitates the migration of immune cells into subarachnoid space. The inflammatory response that ensues is biphasic. In the acute phase, neutrophils, macrophages, and monocytes mediate phagocytosis of free hemoglobin. These cells subsequently degranulate in the subarachnoid space to release pro-inflammatory mediators that contribute to the chronic phase of inflammation, mediated by lymphocytes and macrophages/monocytes [23]. The inflammatory reactions contribute to both neuronal and glial cell death, increased permeability of the blood brain barrier, and microvascular cerebral occlusion resulting in numerous sequelae, including metabolic imbalances, cerebral edema, elevated ICP, cerebral infarcts, vasospasm, and other associated secondary brain injuries.

Given the implication of inflammatory responses in brain injury after SAH, there has been a recent surge of interest in the use of anti-inflammatory medications for treatment after SAH. In experimental models of SAH, drugs aimed at dampening the inflammatory cascade after SAH, including NSAIDs, have been shown to be successful in preventing neurological deterioration [24–27]. These have not, however, been studied in adequately powered human trials. A small study evaluating the efficacy of methylprednisolone administration to 21 patients clinically deemed to be at risk for vasospasm showed reduced rates

Table 2 Clinical outcomes by treatment group

	NSAID ($N = 89$)	Control ($N = 89$)	P value
Death	1 (1.1 %)	8 (8.8 %)	0.034
mRS <2	72 (80.9 %)	61 (68.5 %)	0.083
Angiographic vasospasm			0.610
Severe vasospasm	13 (14.6 %)	16 (18.0 %)	
Moderate vasospasm	30 (33.7 %)	22 (24.7 %)	
Mild vasospasm	9 (10.1 %)	11 (12.4 %)	
No vasospasm	37 (41.6 %)	40 (44.9 %)	
Required rescue therapy	18 (20.2 %)	18 (20.2 %)	1.00
Presence of delayed ischemic neurological deficit	13 (14.6 %)	18 (20.2 %)	0.420
Presence of delayed cerebral ischemia	21 (23.6 %)	26 (29.2 %)	0.496
Total hospital length of stay	45.1 ± 24.1	52.6 ± 27.5	0.053
Days spent in ICU	23.6 ± 17.1	30.8 ± 19.6	0.009
Days spent on ward	21.5 ± 13.61	21.8 ± 15.6	0.897

Data are presented as N (%), mean ± SD, unless otherwise specified

mRS modified Rankin Score, *ICU* intensive care unit

of DIND and improved mortality and neurological outcomes [28]. Moreover, in a randomized, double-blinded, placebo-controlled trial, high doses of methylprednisolone administered after diagnosis of aneurysmal SAH for 3 days significantly improved functional outcome at 1-year follow-up without having an effect on the incidence of symptomatic vasospasm [29]. The use of other immunosuppressants, such as cyclosporine, have not shown benefit in improving outcomes after severe SAH, although there may be a benefit in reducing DINDs if treated early after the aneurysm is secured [30]. Statins have also been shown to have some anti-inflammatory activity [31]; however, a phase III randomized controlled trial of simvastatin treatment for 21 days did not show any benefit in terms of functional outcome, mortality, or adverse events [32].

NSAIDs are a class of medications that have anti-inflammatory, anti-pyretic, and analgesic properties [33]. For this reason, NSAIDs are widely used for patients in the ICU worldwide. NSAIDs partly mediate their anti-inflammatory activity by inhibiting cyclooxygenase (COX) enzymes and therefore by inhibiting prostaglandin synthesis and platelet aggregation [34]. The anti-inflammatory properties of NSAIDs extend beyond cyclooxygenase inhibition and include cytokine level modulation and inhibition of leckocyte-endothelial cell interactions [35, 36]. Ibuprofen, one class of NSAID, has been shown to inhibit intercellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule 1 (VCAM-1) expression in endothelial cells, thereby preventing leukocyte migration into the subarachnoid space [37]. Trials in human subjects have shown that an inverse correlation exists between NSAID use and systemic inflammatory marker levels, and that higher cumulative use of NSAIDs portends a more favorable outcome after SAH [38].

To date, we are only aware of four randomized trials evaluating the efficacy of NSAID use after SAH, three of which were focused on the anti-platelet mechanism of aspirin (ASA). The results of the three trials assessing the efficacy of ASA after SAH together showed that patients treated with ASA treatment had no differences in morbidity, mortality, occurrence of DINDs, and only a slight trend toward improved functional outcomes when compared to controls [39–41]. The fourth randomized trial was a double-blinded, placebo-controlled trial that assessed the efficacy of meloxicam administration within the first 7 days of SAH ictus. The results of this study showed no differences in in-hospital mortality or Glasgow Outcome Scale score on discharge, with a slight trend toward reduced middle cerebral artery velocity in patients treated with meloxicam [42]. Our exploratory analysis is the first to our knowledge to demonstrate that patients who received NSAIDs during their hospital stay after SAH have improved mortality rates and functional outcomes.

There are several putative mechanisms by which NSAIDs may be beneficial after SAH. First, patients may experience a loss of central thermoregulatory mechanisms after SAH; therefore NSAID use may be neuroprotective by helping regulate temperature via their anti-pyretic effects [43]. Second, the anti-platelet aggregation actions of NSAIDs may be neuroprotective by preventing microthrombosis activated by the coagulation cascade following SAH [44]. Interestingly, large-vessel vasospasm and DCI are dissociable phenomena, and increasingly, it is thought that the latter may be mediated by microthrombi

within the cerebral vasculature [44, 45]. This may partly explain why previous studies evaluating the use of NSAIDs after SAH have not shown significant benefit with regard to angiographic vasospasm. Furthermore, serum inflammatory markers and measures of the SIRS have been shown to be correlated with in-hospital non-convulsive seizures, which may lead to neurologic deterioration [11, 46]. It is possible that NSAIDs mitigate the systemic inflammatory response and therefore lead directly to improved outcomes. Future studies evaluating the role of NSAID use after SAH should attempt to elucidate the exact mechanism of benefit.

Our study is limited by the fact that NSAID administration was analyzed collectively despite the fact that different drugs have differing potencies. Unfortunately, unlike steroids, equivalency conversions of the different NSAIDs do not exist. Also, given the exploratory nature of our study, we were unable to stratify patients according to indication for NSAID use. Moreover, we were unable to analyze whether NSAID use was associated with certain adverse events, such as stomach ulcers or infection rates as these variables were not available in the dataset. However, there has been recent data suggesting that the anti-inflammatory effects of NSAIDs may not portend a poor outcome in the setting of infections and may potentially even be beneficial [47–49]. Given that the group treated with NSAIDs had shorter ICU duration and hospital stay duration, it is unlikely that they suffered from major adverse events such as sepsis or GI bleeds from stomach ulcers [50, 51]. The final limitation of our study is that data on duration of NSAID therapy were not available. Our study does provide support for larger prospective trials of anti-inflammatory agents following SAH. Future studies evaluating the efficacy of NSAID use in SAH should attempt to stratify different NSAID medications, their indications, and their doses and should follow the anti-inflammatory effects of NSAIDs using biomarkers of inflammation as outcomes.

Conclusion

In this propensity score-matched analysis, the administration of NSAIDs while in hospital after SAH resulted in reduced mortality and improved functional outcomes. These effects were independent of the development of DIND, DCI, or vasospasm. Furthermore, patients treated with NSAIDs had reduced ICU and hospital lengths of stay. Our findings suggest that inflammation may play a crucial role in the poor outcomes after SAH, and that NSAIDs may be a useful therapeutic option, once validated by larger prospective studies.

Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Disclosure Actelion Pharmaceuticals was the sponsor of the CONSCIOUS-1 trial; the company provided the authors with the anonymized trial data set but had no role in this exploratory analysis nor the development of this article. R.L.M is the chief scientific officer for Edge Therapeutics Inc. R.L.M received grant support from the Physicians Services Incorporated Foundation, Brain Aneurysm Foundation, Canadian Institutes for Health Research, and the Heart and Stroke Foundation of Canada.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individuals included in this study.

References

1. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8(4):355–69.
2. Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. Stroke. 1996;27(9):1459–66.
3. Ayling OG, Ibrahim GM, Drake B, Torner JC, Macdonald RL. Operative complications and differences in outcome after clipping and coiling of ruptured intracranial aneurysms. J Neurosurg. 2015;123(3):621–8.
4. Dorhout Mees SM, Algra A, Vandertop WP, van Kooten F, Kuijsten HA, Boiten J, van Oostenbrugge RJ, Al-Shahi Salman R, Lavados PM, Rinkel GJ, van den Bergh WM, Group M-S. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial. Lancet. 2012;380(9836):44–9.
5. Macdonald RL, Higashida RT, Keller E, Mayer SA, Molyneux A, Raabe A, Vajkoczy P, Wanke I, Bach D, Frey A, Marr A, Roux S, Kassell N. Randomised trial of clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid hemorrhage undergoing surgical clipping (CONSCIOUS-2). Acta Neurochir Suppl. 2013;115:27–31.
6. Zhang S, Wang L, Liu M, Wu B. Tirilazad for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2010;17(2):CD006778.
7. Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, Humphrey PR, Lang DA, Nelson R, Richards P, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. Br Med J. 1989;298(6674):636–42.
8. 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.
9. Muroi C, Hugelshofer M, Seule M, Tastan I, Fujioka M, Mishima K, Keller E. Correlation among systemic inflammatory parameter, occurrence of delayed neurological deficits, and outcome after aneurysmal subarachnoid hemorrhage. Neurosurgery. 2013;72(3):367–75 **discussion 375**.

10. Polin RS, Bavbek M, Shaffrey ME, Billups K, Bogaev CA, Kassell NF, Lee KS. Detection of soluble E-selectin, ICAM-1, VCAM-1, and L-selectin in the cerebrospinal fluid of patients after subarachnoid hemorrhage. J Neurosurg. 1998;89(4):559–67.
11. Tam AK, Ilodigwe D, Mocco J, Mayer S, Kassell N, Ruefenacht D, Schmiedek P, Weidauer S, Pasqualin A, Macdonald RL. Impact of systemic inflammatory response syndrome on vasospasm, cerebral infarction, and outcome after subarachnoid hemorrhage: exploratory analysis of CONSCIOUS-1 database. Neurocrit Care. 2010;13(2):182–9.
12. Ibrahim GM, Morgan BR, Macdonald RL. Patient phenotypes associated with outcomes after aneurysmal subarachnoid hemorrhage: a principal component analysis. Stroke. 2014;45(3):670–6.
13. Macdonald RL, Kassell NF, Mayer S, Ruefenacht D, Schmiedek P, Weidauer S, Frey A, Roux S, Pasqualin A, Investigators C. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. Stroke. 2008;39(11):3015–21.
14. Teasdale GM, Drake CG, Hunt W, Kassell N, Sano K, Pertuiset B, De Villiers JC. A universal subarachnoid hemorrhage scale: report of a committee of the World Federation of Neurosurgical Societies. J Neurol Neurosurg Psychiatry. 1988;51(11):1457.
15. Hijdra A, Brouwers PJ, Vermeulen M, van Gijn J. Grading the amount of blood on computed tomograms after subarachnoid hemorrhage. Stroke. 1990;21(8):1156–61.
16. Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB. Computed tomographic diagnosis of intraventricular hemorrhage. Etiology and prognosis. Radiology. 1982;143(1):91–6.
17. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10(2):150–61.
18. Spallone A, Acqui M, Pastore FS, Guidetti B. Relationship between leukocytosis and ischemic complications following aneurysmal subarachnoid hemorrhage. Surg Neurol. 1987;27(3):253–8.
19. Rousseaux P, Scherpereel B, Bernard MH, Graftieaux JP, Guyot JF. Fever and cerebral vasospasm in ruptured intracranial aneurysms. Surg Neurol. 1980;14(6):459–65.
20. Ascenzi P, Bocedi A, Visca P, Altruda F, Tolosano E, Beringhelli T, Fasano M. Hemoglobin and heme scavenging. IUBMB Life. 2005;57(11):749–59.
21. Clatterbuck RE, Oshiro EM, Hoffman PA, Dietsch GN, Pardoll DM, Tamargo RJ. Inhibition of vasospasm with lymphocyte function-associated antigen-1 monoclonal antibody in a femoral artery model in rats. J Neurosurg. 2002;97(3):676–82.
22. Sabri M, Ai J, Lakovic K, D'Abbondanza J, Ilodigwe D, Macdonald RL. Mechanisms of microthrombi formation after experimental subarachnoid hemorrhage. Neuroscience. 2012;224:26–37.
23. Gallia GL, Tamargo RJ. Leukocyte-endothelial cell interactions in chronic vasospasm after subarachnoid hemorrhage. Neurol Res. 2006;28(7):750–8.
24. Ayer R, Jadhav V, Sugawara T, Zhang JH. The neuroprotective effects of cyclooxygenase-2 inhibition in a mouse model of aneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl. 2011;111:145–9.
25. Chyatte D. Prevention of chronic cerebral vasospasm in dogs with ibuprofen and high-dose methylprednisolone. Stroke. 1989;20(8):1021–6.
26. Frazier JL, Pradilla G, Wang PP, Tamargo RJ. Inhibition of cerebral vasospasm by intracranial delivery of ibuprofen from a controlled-release polymer in a rabbit model of subarachnoid hemorrhage. J Neurosurg. 2004;101(1):93–8.
27. Hakan T, Berkman MZ, Ersoy T, Karatas I, San T, Arbak S. Anti-inflammatory effect of meloxicam on experimental vasospasm in the rat femoral artery. J Clin Neurosci. 2008;15(1):55–9.
28. Chyatte D, Fode NC, Nichols DA, Sundt TM Jr. Preliminary report: effects of high dose methylprednisolone on delayed cerebral ischemia in patients at high risk for vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurgery. 1987;21(2):157–60.
29. Gomis P, Graftieaux JP, Sercombe R, Hettler D, Scherpereel B, Rousseaux P. Randomized, double-blind, placebo-controlled, pilot trial of high-dose methylprednisolone in aneurysmal subarachnoid hemorrhage. J Neurosurg. 2010;112(3):681–8.
30. Manno EM, Gress DR, Ogilvy CS, Stone CM, Zervas NT. The safety and efficacy of cyclosporine A in the prevention of vasospasm in patients with Fisher grade 3 subarachnoid hemorrhages: a pilot study. Neurosurgery. 1997;40(2):289–93.
31. Ascer E, Bertolami MC, Venturinelli ML, Buccheri V, Souza J, Nicolau JC, Ramires JA, Serrano CV Jr. Atorvastatin reduces proinflammatory markers in hypercholesterolemic patients. Atherosclerosis. 2004;177(1):161–6.
32. Kirkpatrick PJ, Turner CL, Smith C, Hutchinson PJ, Murray GD, Collaborators S. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol. 2014;13(7):666–75.
33. Green GA. Understanding NSAIDs: from aspirin to COX-2. Clin Cornerstone. 2001;3(5):50–60.
34. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232–5.
35. Diaz-Gonzalez F, Sanchez-Madrid F. Inhibition of leukocyte adhesion: an alternative mechanism of action for anti-inflammatory drugs. Immunol Today. 1998;19(4):169–72.
36. Hamza M, Dionne RA. Mechanisms of non-opioid analgesics beyond cyclooxygenase enzyme inhibition. Curr Mol Pharmacol. 2009;2(1):1–14.
37. Kapiotis S, Sengoelge G, Sperr WR, Baghestanian M, Quehenberger P, Bevec D, Li SR, Menzel EJ, Muhl A, Zapolska D, Virgolini I, Valent P, Speiser W. Ibuprofen inhibits pyrogen-dependent expression of VCAM-1 and ICAM-1 on human endothelial cells. Life Sci. 1996;58(23):2167–81.
38. Muroi C, Hugelshofer M, Seule M, Keller E. The impact of nonsteroidal anti-inflammatory drugs on inflammatory response after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2014;20(2):240–6.
39. Hop JW, Rinkel GJ, Algra A, Berkelbach van der Sprenkel JW, van Gijn J. Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. Neurology. 2000;54(4):872–8.
40. van den Bergh WM, Group MS, Algra A, Dorhout Mees SM, van Kooten F, Dirven CM, van Gijn J, Vermeulen M, Rinkel GJ. Randomized controlled trial of acetylsalicylic acid in aneurysmal subarachnoid hemorrhage: the MASH study. Stroke. 2006;37(9):2326–30.
41. Mendelow AD, Stockdill G, Steers AJ, Hayes J, Gillingham FJ. Double-blind trial of aspirin in patient receiving tranexamic acid for subarachnoid hemorrhage. Acta Neurochir (Wien). 1982;62(3–4):195–202.
42. Ghodsi SM, Mohebbi N, Naderi S, Anbarloie M, Aoude A, Habibi Pasdar SS. Comparative efficacy of meloxicam and placebo in vasospasm of patients with subarachnoid hemorrhage. Iran J Pharm Res. 2015;14(1):125–30.
43. Broessner G, Beer R, Lackner P, Helbok R, Fischer M, Pfausler B, Rhorer J, Kuppers-Tiedt L, Schneider D, Schmutzhard E. Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease: bicenter prospective, randomized trial. Stroke. 2009;40(12):e657–65.

44. Vergouwen MD, Vermeulen M, Coert BA, Stroes ES, Roos YB. Microthrombosis after aneurysmal subarachnoid hemorrhage: an additional explanation for delayed cerebral ischemia. J Cereb Blood Flow Metab. 2008;28(11):1761–70.
45. Tso MK, Macdonald RL. Subarachnoid hemorrhage: a review of experimental studies on the microcirculation and the neurovascular unit. Transl Stroke Res. 2014;5(2):174–89.
46. Claassen J, Albers D, Schmidt JM, De Marchis GM, Pugin D, Falo CM, Mayer SA, Cremers S, Agarwal S, Elkind MS, Connolly ES, Dukic V, Hripcsak G, Badjatia N. Nonconvulsive seizures in subarachnoid hemorrhage link inflammation and outcome. Ann Neurol. 2014;75(5):771–81.
47. Legras A, Giraudeau B, Jonville-Bera AP, Camus C, Francois B, Runge I, Kouatchet A, Veinstein A, Tayoro J, Villers D, Autret-Leca E. A multicentre case-control study of nonsteroidal anti-inflammatory drugs as a risk factor for severe sepsis and septic shock. Crit Care. 2009;13(2):R43.
48. Aronoff DM, Bloch KC. Assessing the relationship between the use of nonsteroidal antiinflammatory drugs and necrotizing fasciitis caused by group A streptococcus. Medicine. 2003;82(4):225–35.
49. Eisen DP. Manifold beneficial effects of acetyl salicylic acid and nonsteroidal anti-inflammatory drugs on sepsis. Intensive Care Med. 2012;38(8):1249–57.
50. Czymek R, Grossmann A, Roblick U, Schmidt A, Fischer F, Bruch HP, Hildebrand P. Surgical management of acute upper gastrointestinal bleeding: still a major challenge. Hepatogastroenterology. 2012;59(115):768–73.
51. Chua SK, Liao CS, Hung HF, Cheng JJ, Chiu CZ, Chang CM, Lee SH, Lin SC, Liou JY, Lo HM, Kuan P, Shyu KG. Gastrointestinal bleeding and outcomes after percutaneous coronary intervention for ST-segment elevation myocardial infarction. Am J Crit Care. 2011;20(3):218–25.