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ORIGINAL ARTICLE

The Impact of Nonsteroidal Anti-inflammatory Drugs on Inflammatory Response After Aneurysmal Subarachnoid Hemorrhage

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Abstract
Background The degree of inflammatory response with cytokine release is associated with poor outcomes after aneurysmal subarachnoid hemorrhage (SAH). Previously, we reported on an association between systemic IL-6 levels and clinical outcome in patients with aneurysmal SAH. The intention was to assess the impact of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen on the inflammatory response after SAH.
Methods Our method involved exploratory analysis of data and samples collected within a previous study. In 138 patients with SAH, systemic interleukin (IL-6) and c-reactive protein (CRP) were measured daily up to day 14 after SAH. The correlations among the cumulatively applied amount of NSAIDs, inflammatory parameters, and clinical outcome were calculated.
Results An inverse correlation between cumulatively applied NSAIDs and both IL-6 and CRP levels was found ($r = -0.437$, $p < 0.001$ and $r = -0.369$, $p < 0.001$ respectively). Multivariable linear regression analysis showed a cumulative amount of NSAIDs to be independently predictive for systemic IL-6 and CRP levels. The cumulative amount of NSAIDs reduced the odds for unfavorable outcome, defined as Glasgow outcome scale 1–3.
Conclusions The results indicate a potential beneficial effect of NSAIDs in patients with SAH in terms of ameliorating inflammatory response, which might have an impact on outcome.

Keywords Nonsteroidal anti-inflammatory drugs · Inflammation · Subarachnoid hemorrhage · Interleukin-6

Introduction

Considerable advances in diagnosis, surgical treatment, and neurocritical care medicine have reduced the risk of mortality after aneurysmal subarachnoid hemorrhage (SAH). However, the functional outcome remains poor in these patients [1]. Ample evidence derived from experimental settings suggests that inflammatory pathways with cytokine release, such as interleukin-6 (IL-6), are involved in the pathogenesis of cerebral injury [2–4]. Recently, we reported on a positive correlation between systemic IL-6 levels and poor outcomes in patients with SAH [5]. Several drugs, including nonsteroidal anti-inflammatory drugs (NSAIDs), aimed at limiting the inflammatory response, have been experimentally validated, with varying levels of success [2, 6–11]. However, clinical studies specifically examining the effect of NSAIDs on inflammatory response and outcome after SAH are virtually nonexistent. The present study intended to elucidate the potential impact of NSAID application—including acetaminophen—on inflammatory parameters, in particular IL-6 levels, in the acute phase after SAH [5].

Materials and Methods

The current study is an exploratory analysis of data and samples collected within a previous study [5]. In brief, the

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prospective observational study was carried out at a single academic tertiary care center during a 3-year period. Because of its purely exploratory design, a sample size calculation was not determined. The study was approved by the local ethics committee. All patients with confirmed aneurysmal SAH were included. The diagnosis was based on CT and angiography studies. Exclusion criteria included admission >3 days after ictus, uncertain time of ictus, death within 3 days after admission, and conservative or delayed aneurysm treatment. The severity at time of admission was assessed based on the World Federation of Neurological Surgeons (WFNS) grading. All patients were treated according to a standardized treatment protocol as previously described [5, 12–14]. In all patients, mean arterial blood pressure (MAP) was monitored by an arterial catheter. MAP was held constant within the range of 80–120 mmHg after aneurysm securement. Blood glucose concentration was measured at least q 4 h and was held constant within the range of 5–8 mmol/ml. In intubated and ventilated patients, arterial pO_2 and pCO_2 were measured at least q 4 h and kept within the following range: paO_2: >12.0 kPa; and pCO_2: 4.8–5.6 kPa. The duration of sedation was kept as short as possible. Indications for long-term sedation are intracranial hypertension and/or severe cardiac or respiratory failure. Core body temperature ≥38 °C was regarded as fever and was treated accordingly. NSAID prescription in general was at the discretion of the attending neurointensivist on duty, based on a stepwise management scheme starting with acetaminophen (INN, paracetamol) followed by dipyrone (INN, metamizol), diclofenac, and ibuprofen. Contraindication for acetaminophen was pathologically high lever enzymes. Known ulcer diseases, erosive gastritis or colitis, coagulation disorders, and unsecured aneurysms were contraindications for ibuprofen and diclofenac. Dosages were adapted to body weight and kidney function. Maximum dosages per day were 4 g for acetaminophen, 4 g for dipyrone, 150 mg for diclofenac, and 2.4 g for ibuprofen. As for the inflammatory parameter, daily systemic c-reactive protein (CRP) and IL-6 levels were measured in terms of clinical routine from day 3 to 14 after SAH. Physiological IL-6 and CRP levels were <3.3 ng/l and <5 mg/l, respectively. Blood sampling was performed early in the morning between 06:30 and 07:30 h. The samples underwent no freeze–thaw cycle as the samples were analyzed once immediately by the Institute of Clinical Chemistry, University Hospital Zurich. IL-6 and CRP levels were not an integral part of the NSAID management scheme. The principal investigator (C.M.) was not a treating physician and did not have any influence on NSAID prescription.

Infectious complications were assessed as confounding factors, as they influence the level of inflammatory parameters [15]. Criteria for the presence of an infectious complication are summarized in Table 1. Having a potential impact on inflammatory serum parameters as well as on prescription of NSAIDs, the application of mild therapeutic hypothermia (intravascular catheter-based heat exchange system, Zoll Medical, Chelmsford, MA, USA; target brain temperature 33–34 °C) was also included in the analysis. Indications for hypothermia included elevated intracranial pressure and/or symptomatic CVS refractory to conventional treatment [16]. Having a direct impact on outcome, the occurrence of cerebral infarction was assessed as a confounding factor [17]. Cerebral infarction was defined as new ischemic lesions, which could not be attributed to surgery or endovascular intervention. All patients had a baseline cranial computed tomography. Further scans were obtained within 24 h after the aneurysm-securing procedure, at discharge, and if the patient had neurological worsening. The clinical outcome was assessed 3 months after SAH in the outpatient clinic, based on the Glasgow outcome scale (GOS).

Categorical variables were described using frequency and percentage. WFNS grades were dichotomized into non-severe (WFNS 1–3) and severe (WFNS 4–5), GOS scales into unfavorable (GOS 1–3) and favorable (GOS 4–5). Continuous variables were described as median and quartiles if not otherwise indicated. As IL-6 and CRP levels showed a high variance, the values were logarithmically transformed for statistical analysis. A variable "cumulative NSAID days" was defined for semi-quantification and represents the sum of days (until day 14 after SAH) where the patients received NSAID, multiplied by the number of different NSAIDs including acetaminophen. This methodological simplification was performed as quantitative equivalent conversion is not possible for NSAIDs. Occurrence of fever was quantified as febrile days, defined as exceeding threshold core body temperature ≥38 °C for >1 h at least once per day.

Pearson's correlation coefficient between median values of inflammatory markers and cumulative NSAID days was

Table 1 Criteria for infectious complications

Pneumonia	Specific signs of alveolar infiltrate on chest X-ray and microorganism isolated from tracheobronchial secretion cultures[a]
Blood stream infection	Predominant microorganism identified in blood cultures[a]
Urinary tract infection	Isolation of $>10^5$ microorganisms/ml in urinary cultures[a]
Catheter-related infection	Isolation of $>10^5$ colony-forming units from catheter tips[a]
CSF infection	Pleocytosis with positive microbiological cultures

CSF cerebrospinal fluid

[a] cultures were only obtained in the setting of suspected infection

calculated. A linear regression analysis was performed to assess the effect of NSAIDs on inflammatory parameters unadjusted and adjusted for confounding variables. Applications of therapeutic hypothermia, WFNS grade, occurrence of infectious complications, and occurrence of fever were considered as possible confounding factors. The correlation between NSAID days and binominal variables was calculated by a point-biserial correlation analysis. To investigate whether the application of NSAIDs had an impact on outcome, an unconditional logistic regression, unadjusted and adjusted for confounding covariates, was performed. Age, WFNS grade, occurrence of cerebral infarctions, and fever were defined as confounding factors, representing generally accepted, clinically meaningful predictors in patients with SAH [17–20]. For the significant factors, odds ratios (OR) and their 95 % confidence intervals (CI) were calculated. A p value <0.05 was regarded as statistically significant. IBM SPSS Statistics 20.0 Software was used.

Results

Of the 209 patients with SAH admitted to the Neurocritical Care Unit, University Hospital of Zurich, during the 3-year period, 138 patients were analyzed in the present study. Exclusion criteria were met in 71 patients. The patients' characteristics are shown in Table 2. Fifty patients (36 %) received 2, 38 patients (28 %) received 3, and 12 patients (9 %) received 4 different types of NSAIDs. Eleven patients (8 %) received 1 single type of NSAID. The most frequent NSAID was acetaminophen followed by dipyrone, diclofenac, and ibuprofen. Overall median cumulative NSAID days were 15.5 (range 0–42), 20 (range 0–42) in patients without and 2 (range 0–19) in patients with therapeutic hypothermia. The difference was statistically highly significant ($p < 0.001$, Mann–Whitney test). In the majority of these cases, application of NSAIDs decreased dramatically as soon as the target temperature was achieved and maintained. Quantitatively, an inverse correlation could be found between cumulative NSAID days and number of days with hypothermia ($r = -0.677$, $p < 0.001$). The analysis of the correlation between cumulative NSAID days and IL-6 established an inverse correlation ($r = -0.437$, $p < 0.001$) (Fig. 1a). Furthermore, there was also a weaker inverse correlation between the cumulative NSAID days and CRP ($r = -0.369$, $p < 0.001$) (Fig. 1b). A subgroup analysis showed a correlation in patients without hypothermia ($r = -0.504$, $p < 0.001$ for IL-6 and $r = -0.326$, $p < 0.001$ for CRP), while no correlations could be found in patients with hypothermia. Due to the weaker anti-inflammatory properties of acetaminophen, a subanalysis was performed without acetaminophen: The correlation between cumulative NSAID days (without acetaminophen) and IL-6 and CRP was $r = -0.409$, $p < 0.001$ and $r = -0.327$, $p < 0.001$, respectively. The correlations were weaker than with acetaminophen. A weak positive correlation between IL-6 and number of febrile days was found ($r = 0.198$, $p = 0.02$), while a correlation between CRP and number of febrile days could not be found ($r = 0.134$, $p = 0.12$). The partial correlation coefficient between cumulative NSAID days and IL-6/CRP, adjusted for febrile days, was stronger than the previous unadjusted coefficients ($r = -0.484$, $p < 0.001$ for IL-6 and $r = -0.400$, $p < 0.001$ for CRP). Analyzing the correlation between occurrence of cerebral infarction and cumulative NSAID days, a weak inverse correlation was found ($r = -0.222$, $p < 0.010$). A moderate inverse correlation was found between cumulative NSAID days and dichotomized outcome ($r = -0.365$, $p < 0.001$). This correlation remained present after exclusion of patients receiving therapeutic hypothermia ($r = -0.244$, $p = 0.013$). We also found an inverse correlation between WFNS grade and cumulative NSAID days ($r = -0.409$, $p < 0.001$). As shown in Table 3, linear regression analysis showed cumulative NSAID days to be predictive for systemic IL-6 and CRP levels in an inverse manner, unadjusted and adjusted for confounding factors. In the logistic regression analysis, the variable cumulative NSAID days were revealed to be an inverse predictor for poor outcome (GOS 1–3): OR 0.918 (95 % CI 0.880–0.956, $p < 0.001$). After exclusion of patients receiving therapeutic hypothermia, the variable cumulative NSAID remained an inverse predictor for poor outcome: OR 0.932 (95 % CI 0.881–0.897, $p = 0.016$). After adjustment for confounding factors (WFNS grade, occurrence of cerebral infarction, age, and febrile days), cumulative NSAID days remained an independent inverse predictor for poor outcome: OR 0.921 (95 % CI 0.870–0.975, $p = 0.005$). The inclusion of aneurysm treatment modality in the regression analyses did not alter the result. The adjusted OR is shown in Table 4. Logistic regression analysis showed the variable cumulative NSAID days to be an inverse predictor for the occurrence of cerebral infarction as well: OR 0.933 (95 % CI 0.884–0.986, $p = 0.013$).

Discussion

The present study established an inverse relationship between the amount of NSAIDs applied and systemic inflammatory parameters (IL-6 and CRP) in the acute phase (≤day 14) after SAH. Linear regression analysis showed that the amount of NSAIDs applied was predictive for lower IL-6 and CRP levels after adjustment for potentially confounding factors. These results are of

Table 2 Patients' characteristics

	Total ($n = 138$)
Age, y, mean ± SD	55.3 ± 12.9
Sex	
Female, *n* (%)	91 (66 %)
Male, *n* (%)	47 (34 %)
WFNS Grade	
1–3, *n* (%)	91 (66 %)
4–5, *n* (%)	47 (34 %)
Aneurysm treatment	
Clipping	78 (56 %)
Coiling	60 (44 %)
Temp. ≥38 °C, days, median (range)	2.54 (0–10)
Therapeutic hypothermia	
No hypothermia, *n* (%)	103 (75 %)
Hypothermia, *n* (%)	35(25 %)
Infectious complications	
No infection	63 (46 %)
Infection	75 (54 %)
Cerebral infarction	
Cerebral infarction	19 (14 %)
No cerebral infarction	115 (85 %)
Outcome (GOS)	
Favorable (GOS 4–5), *n* (%)	94 (68 %)
Unfavorable (GOS 1–3), *n* (%)	44 (32 %)
Inflammatory Parameter	
IL-6, ng/l, median (*Q*1; *Q*3)	7.7 (4.2; 13.8)
CRP, mg/l, median (*Q*1; *Q*3)	23 (12; 40)

SD standard deviation, *Temp.* core body temperature, *Q1* under quartile, *Q3* upper quartile

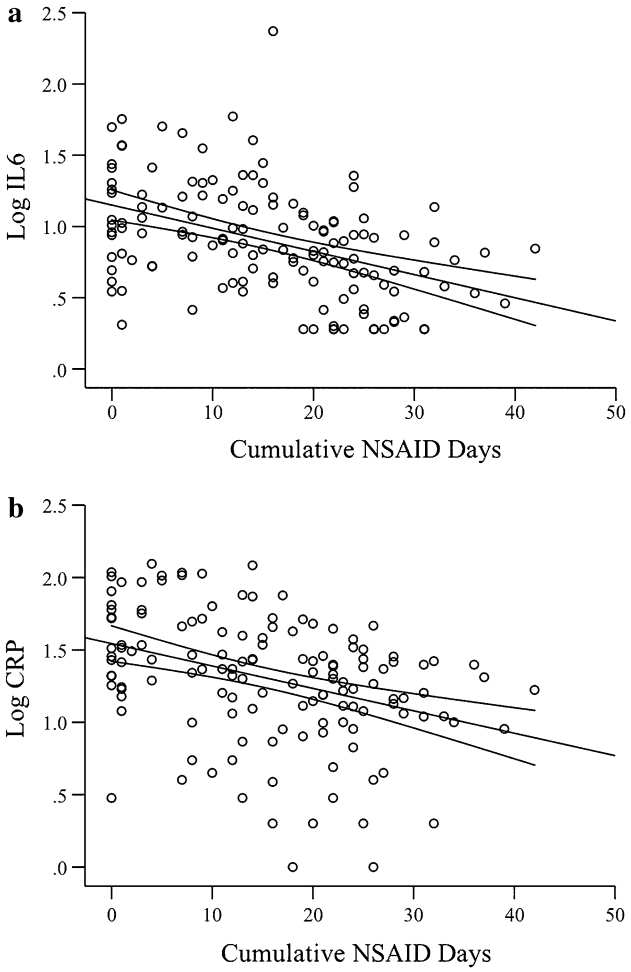

Fig. 1 Inverse correlations of cumulative NSAID days and log IL-6 A) and CRP B) shown as scatterplots. **a** Pearson's correlation $r = -0.437$ ($p < 0.001$) and **b** $r = -0.369$ ($p < 0.001$)

interest, as high CRP and IL-6 levels in particular have been associated with worse neurological outcomes in patients with SAH [3, 5, 21]. In the logistic regression analysis, the cumulative amount of NSAIDs reduced the odds for worse functional outcome. Although the occurrence of fever was correlated to some extent, the effect of NSAIDs on inflammatory markers as well as neurological outcome could not be attributed to the effect of fever alone in our statistical model. While age, severity of SAH, and occurrence of cerebral infarction are well-accepted risk factors for worse outcome [18, 19], the relation between NSAID application and outcome is a rather new aspect. This positive impact on the outcome might be partially related to the decrease in the occurrence of cerebral infarctions. However, based on the multivariable regression analysis, NSAID acts beneficially independent from its ability to avoid the occurrence of cerebral infarctions.

An additional observation of interest is the influence of the application of therapeutic hypothermia on the prescription of NSAIDs. The prescription of NSAIDs decreased dramatically as soon as therapeutic hypothermia was induced. Although induction and maintenance of hypothermia were strictly based on a protocol [14], we were not consciously aware of the fact that the application of hypothermia led to a decreased prescription of NSAIDs, as this aspect was not considered in the protocol up to date.

Classical NSAIDs applied in the current patient population are diclofenac and ibuprofen, both unselective COX inhibitors. They mainly exert their anti-inflammatory and analgesic properties by inhibiting the cyclooxygenase (COX)-2 pathway. COX-2 enzymes synthesize proinflammatory prostaglandins (PG). However, they also have an inhibitory effect on COX-1, which is constitutively expressed in platelets and is responsible for the formation of proaggregatory thromboxane A2. Acetaminophen is often claimed to possess no or only weak anti-inflammatory properties. Therefore, it is generally not considered as

Table 3 Linear regression analysis

	B	95 % CI		Sig.	*B*	95 % CI		Sig.
		Upper	Lower			Upper	Lower	
	Dependent variable: Log IL-6				Dependent variable: Log CRP			
Cumulative NSAID days	−0.016*	−0.022	−0.011	$p < 0.001$	−0.015*	−0.022	−0.009	$p < 0.001$
	−0.019†	−0.026	−0.012	$p < 0.001$	−0.014†	−0.023	−0.005	$p = 0.002$

CI confidence interval, *Sig.* significance

* unadjusted coefficient

† adjusted for application of therapeutic hypothermia, WFNS grade, occurrence of infectious complications, and fever

Table 4 Logistic regression analysis for unfavorable outcome

	OR	95 % CI		Sig.
		Upper	Lower	
Cumulative NSAID days	0.924	0.873	0.979	$p = 0.007$
Age (years)	1.055	1.014	1.098	$p = 0.008$
Febrile days	1.007	0.85	1.194	$p = 0.935$
WFNS 1–3	Reference category			
WFNS 4–5	0.321	0.122	0.846	$p = 0.022$
No cerebral infarction	Reference category			
Cerebral infarction	0.348	0.112	1.077	$p = 0.067$
Coiling	Reference category			
Clipping	0.582	0.241	1.403	$p = 0.228$

OR (adjusted) odds ratio, *CI* confidence interval, *Sig.* significance

a NSAID. However, it is noteworthy that this statement is based largely on early works showing that acetaminophen does not suppress inflammation associated with rheumatoid arthritis, whereas anti-inflammatory action has been supported in different types of inflammatory conditions and the mechanism of action has been suggested to be its highly selective COX-2 inhibition [22]. A more contemporary study suggests a reinvestigation of acetaminophen in terms of anti-inflammatory mechanisms [22]. Furthermore, the drug has always been associated with a suppression of PG synthesis in the CNS [22]. Based on our results, it might be assumed that acetaminophen has some effect on the inflammatory response, as the correlations of cumulative NSAID days with IL-6 and CRP were weaker without acetaminophen. Another NSAID drug that was included in the analysis was dipyrone, which has pronounced analgesic and antipyretic effects, but weak anti-inflammatory effects as well [23]. Although its mechanism of action is not entirely clear, it elicits substantial inhibition of COX in humans. With respect to the COX inhibition, NSAIDs are reported to act via other mechanisms such as inhibition of leukocyte–endothelial cell interaction or modulation of cytokine expressions, including IL-6 [24, 25].

Due to the potential inhibitory effect on platelet aggregation, some neurosurgeons and neurointensivists might be reluctant to apply NSAIDs for analgesic and antipyretic purposes after SAH [26–28]. However, there is no evidence that administration of NSAIDs carries a higher risk for rebleeding and consecutive worse outcome. In the current study, no intracranial rebleedings attributable to excessive NSAIDs' application could be identified. On the one hand, there are virtually no consensus and guidelines with regard to pain management and application of NSAIDs [26–28]. On the other hand, according to the international multidisciplinary consensus conference on the critical care management of SAH, the application of NSAIDs is considered to be the first-line intervention in order to control hyperthermia [20]. There is certainly a strong rationale to avoid fever, as it has been repeatedly connected to worse outcome [20]. As central thermoregulation might be hampered after SAH, NSAIDs might not be effective enough though. Advanced temperature controlling using cooling devices—cooling blankets or an intravascular heat exchange catheter—might be more effective in these cases. More recently, Broessner et al. [29] compared the effectiveness of endovascular cooling to maintain normothermia with standardized, stepwise, escalating fever management in patients with ischemic or hemorrhagic stroke: Long-term, catheter-based, prophylactic normothermia significantly reduced fever burden. Interestingly, CRP and IL-6 levels were significantly higher, while the application of NSAIDs was significantly lower in the device group compared to the controls. A subgroup analysis revealed that application of NSAIDs led to a significant decrease of CRP in patients with endovascular cooling. The authors argued that the combination of advanced temperature controlling with NSAIDs might have additional neuroprotective effects [30]. This has yet to be proven.

There is increasing evidence that the degree of inflammatory response is associated with occurrence of secondary ischemic events and/or worse outcome after SAH [2, 3, 5]. Therefore, there is a strong rationale to suppress inflammatory response. In animal experimental studies, NSAIDs

have been shown to prevent CVS or brain edema after SAH, either by COX inhibition or other mechanisms such as inhibition of leukocyte–endothelial cell interactions [6–8, 10, 31, 32], while dipyrone has been found to be remarkably neuroprotective in experimental cerebral ischemia [33].

In theory, the potential inhibitory effect of NSAIDs on platelet aggregation might act beneficial too as activation of the coagulation cascade and occurrence of microthrombosis have been discussed to contribute to the pathogenesis of cerebral infarction [34]. Clinical studies with antiplatelet therapies showed a trend toward improved outcome. However, no definite conclusions could be drawn. On the basis of the current evidence, routine treatment with antiplatelet agents in order to prevent cerebral infarction or poor outcome is currently not recommended [35]. There are virtually no clinical trials specifically aimed at investigating the role of NSAID on inflammatory response in patients with SAH. To the best to our knowledge, only acetylic acid (ASA)—an NSAID with irreversible COX inhibition—has been clinically evaluated in a controlled randomized trial. However, the trial was conducted with the anti-aggregatory effect of ASA in mind, and not with regard to its anti-inflammatory effect. The trial did not confirm a beneficial effect of rectal ASA administration on the occurrence of delayed ischemic neurological deficit. However, the functional outcome in patients who received ASA tended to be better [36].

Hypothermia might exert its neuroprotective properties by attenuation of destructive inflammatory reactions. Mild hypothermia has been shown to reduce proinflammatory cytokine levels such as IL-6 after different types of brain insults, including SAH [16, 37, 38]. As patients with therapeutic hypothermia need deep analgosedation, there might be no objective to administer NSAIDs for fever and pain management. However, the combination of NSAIDs and mild hypothermia might have synergistic anti-inflammatory and neuroprotective effects. This calls for further examinations, as the answer to the latter question is beyond the possibilities of the present study due to its limited sample size and observational nature.

A clear shortcoming of the current study is the fact that different types of NSAIDs were lumped together for analysis, despite their different anti-inflammatory potencies. However, this methodological simplification was performed as quantitative equivalent conversion is not possible, in contrast to corticosteroids. A separated subanalysis for each medication was regarded as questionable as all medications were applied in a stepwise management scheme. Further, the drugs mentioned were used not only as antipyretics but also for pain treatment, and the detailed discrimination between the two indications could not be performed due to methodological reasons. Patients with a better level of consciousness would be expected to both need more painkillers and have better outcomes than patients in coma. The inverse correlation between WFNS grade and cumulative amount of NSAIDs we found supports this assumption. However, based on the results of the regression analysis, the amount of NSAIDs remained an independent predictor for poor outcome. It also has to be mentioned that the predetermined exclusion criteria might have biased the current results [5]. Another shortcoming is the fact that only systemic inflammatory markers were measured. It would be of great interest to additionally measure intrathecal inflammatory markers to assess the impact of NSAIDs, with or without hypothermia, on the compartmental inflammatory response within the CNS. Finally, the actual mechanism by which NSAIDs influenced both inflammatory parameters and outcome cannot be answered.

Conclusions

The results of the current study indicate an inverse correlation between the amounts of NSAIDs applied and systemic IL-6 and CRP levels in patients with SAH. A higher amount of NSAID application reduced the odds for unfavorable outcome. In the present study, therapeutic hypothermia led to a significant decrease of NSAID application. In the case of using cooling devices to induce normo- or hypothermia, the question arises whether to continue with NSAID application or not, as it might act in a synergistic manner in terms of ameliorating inflammation.

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Conflict of interest Carl Muroi, Michael Hugelshofer, Martin Seule, and Emanuela Keller declare that they have no conflict of interest.

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