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Evaluation of headache severity after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Objective: The most common complaint from patients after subarachnoid hemorrhage (SAH) is headache. The headache appears to be persistent and often severe. Although this problem is pervasive in the care of SAH patients, very little data have been published to describe the nature and severity of the headache nor is there evidence-based guidance on the appropriate treatment of headache due to SAH.

Methods: This was a retrospective medical record review of adults with aneurysmal SAH. Basic demographics, along with pain scores and analgesic medication administration, were collected. Patients with early vasospasm (within 7 days of ictus) were compared with patients with no vasospasm.

Results: The patient population was characteristic of the typical SAH population. Approximately 31.5% of patients exhibited early vasospasm. These patients had higher pain scores (median 8/10) than did patients without vasospasm (median 6/10) and required more analgesics such as acetaminophen/butalbital/caffeine. Treatment success with any analgesic used in this population was minimal. The pain scores associated with headache increased over the first 7 days in both groups.

Conclusions: Headache after SAH is persistent and treatment refractory. There may be an association with development of vasospasm and worsening of headache. Novel treatment strategies to attenuate headache in this population are needed.

Introduction

Headache is the most common complaint of patients who present with aneurysmal subarachnoid hemorrhage (SAH) [1]. It is thought that the headache is primarily due to the chemical irritation of the blood on the brain meninges, though many other factors are associated (Fig. 1). The hypertension that tends to be present after SAH may also contribute to the development of headache, as may the evolution of cerebral vasospasm and hydrocephalus which may develop as a consequence of SAH. Very little data exist regarding the severity and treatment of headache after SAH, which likely lead to a wide variety in practice. In fact, only one published report of headache treatment in SAH patients is available [2].

Many of the commonly used analgesics for headache are problematic in the acute SAH patient. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit platelet aggregation, thereby exacerbating bleeding after SAH. Opioid medications such as oxycodone or morphine can cause sedation, which may confound the neurologic exam in these vulnerable patients. Alternative, non-opioid agents such as tramadol also cause sedation and may reduce seizure threshold [3,4]. Combination agents such as acetaminophen/butalbital/caffeine (Fioricet) may have various adverse effects and variable durations of action (eg. caffeine can cause cerebral vasoconstriction, but has a short half-life; Butalbital causes sedation and has a very prolonged half-life) [5,6]. Other agents such as magnesium and dexamethasone have also been used for SAH patients [2]. Magnesium may cause hypotension with rapid administration, while dexamethasone (like all corticosteroids) is associated with a number of adverse effects (most concerning acutely are hyperglycemia and agitation). Clinicians are often left with few evidence-based options for treating headache, the most prevalent of which is acetaminophen (which, in doses >4 g/day may cause hepatic dysfunction).

The purpose of the present study was to describe the severity and progression of early headache after SAH (within the first 7 days of ictus) and to evaluate headache treatment patterns in our patient population.

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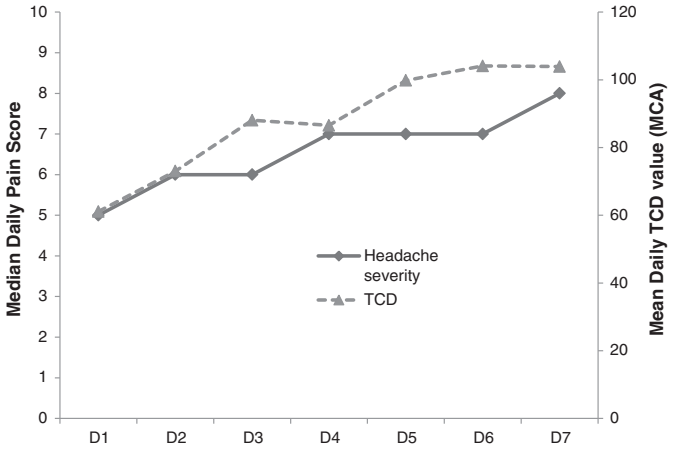

Fig. 1. Daily headache pain scores and TCD measurements.

Materials and methods

The study was a retrospective medical chart review of adult inpatients admitted to the University of Kentucky Chandler Hospital with aneurysmal SAH. The University Health Consortium (UHC) database was used to identify patients with the diagnosis code for a SAH admitted to the University of Kentucky Chandler Hospital between July 2008 and December 2010. Patients were included if they had an aneurysmal SAH and a hospital length of stay of at least 3 days. Patients were excluded if their SAH was due to trauma, if they had inadequate medication administration records or incomplete medical records, or if they presented with Hunt and Hess Grade V SAH [7]. Grade V SAH patients were excluded due to the relative lack of qualitative assessment of pain in these patients by the nursing staff. Local institutional review board approval was obtained via expedited review.

The primary outcome of the study was to evaluate the pain scores associated with headache in patients within seven days of a SAH. Secondary outcomes included a description of the use of analgesic medications for the treatment of headache within the same time period and the incidence of early vasospasm as it related to headache. Data points that were collected included patient demographic data, SAH characteristics (location, severity, method of embolization), total analgesic dose per day for the first seven days after ictus, daily maximum pain scores (standardized score of one to ten), presence of clinical vasospasm as dictated in daily physician progress notes, cerebral blood flow velocity measurements (via transcranial Dopplers (TCDs)), and pertinent laboratory values.

Management of SAH patients in our institution is consistent with published guidelines [8]. Specifically, blood pressure is rigorously controlled upon admission (typical goal is systolic blood pressure < 140–150 mmHg). Nimodipine 60 mg PO/per tube q4 h and atorvastatin 80 mg PO/per tube daily are initiated on hospital day 1. Digital subtraction angiography is performed as soon as is feasible to describe the location and morphology of the aneurysm and aneurysms are secured via endovascular coiling or surgical clipping as soon as possible. After the aneurysm is secured, patients are kept euvolemic and the blood pressure is typically permitted to rise to no greater than a systolic blood pressure of 180 mmHg. TCDs are evaluated daily. Sedating medications are avoided whenever possible. SAH patients typically reside in the intensive care unit for frequent and, often invasive, monitoring. Pain scores (on a 10-point analog scale) are monitored routinely. Magnesium concentrations are routinely monitored and serum concentrations are generally targeted to be in the normal range (2–2.8 mg/dl). Vasospasm was defined as clinical symptoms or radiographic findings as judged by the attending physician and documented in the medical record.

For the primary outcome, a univariate analysis was used to determine if there is an association between the presence of vasospasm and the amount of Fioricet® in tablets per day administered. A two sample t-test was used for interval/ratio data and the Chi squared test was used for categorical variables. Multivariate logistic regression was used to model the odds of vasospasm among patients with Fioricet® exposure, adjusting for age and SAH severity (as measured by Hunt and Hess Score) [9]. We dichotomized Hunt and Hess Score into groups of 1–2 and 3–4 for the purposes of the multivariate analysis [10,11]. Data analysis was conducted using SAS, v.9.3; an alpha level of 0.05 was used throughout.

Results

The UHC database identified 244 patients who were admitted with a SAH within the designated time period. Of those patients, 136 patients were excluded. The top reasons for exclusion included a length of hospitalization less than 3 days or Hunt and Hess Grade V SAH on presentation. Of the 108 patients who were included within the analysis, 34 patients (31.5%) experienced vasospasm within

Table 1
Patient demographics.

	Total (n=108)	Vasospasm (n=34)	No vasospasm (n=74)	P-value
Age (years) Mean(S.D)	52.3 (13.1)	48.7 (11.8)	54.6 (12.6)	0.02
Gender (n, % female)	68 (63.1%)	25 (73.5%)	43 (58.1%)	0.123
Weight (kg) Mean (S.D.)	81.7 (27)	80.9 (21.1)	82.9 (29.4)	0.726
History of tobacco use (n, %)	69 (63.6%)	23 (67.6%)	45 (61.6%)	0.494
Presenting Hunt & Hess score Median (IQR)	2 (0)	2 (1)	2 (0)	0.21
Method of aneurysm embolization				
Clipping	12 (11.1%)	5 (14.7%)	7 (9.5%)	
Coiling	59 (54.6%)	20 (58.8%)	39 (52.7%)	
None	37 (34.3%)	9 (26.5%)	28 (37.8%)	
N, (%)				
ICU length of stay (days) Mean (S.D.)	4.5 (7)	8 (9)	4 (5)	0.002
Hospital length of stay (days) Mean (S.D.)	9 (7)	13.5 (7.75)	9 (5)	0.004
Discharge disposition				
Home	87 (80.6%)	24 (70.6%)	63 (85.1%)	
Acute rehabilitation	15 (13.9%)	8 (23.5%)	7 (9.5%)	
Long-term care facility	3 (2.8%)	0 (0%)	3 (4.1%)	
Deceased	3 (2.8%)	2 (5.9%)	1 (1.4%)	

7 days after the SAH. Table 1 provides detailed information regarding patient characteristics and the treatment of their SAH. Generally, the population was comparable to previously described SAH patients [12,13]. Most patients were female (63.1%), with a mean age of 52.8 years, and a high prevalence of smoking (63.6%). Many of the patients underwent endovascular coiling for their aneurysm and had a prolonged hospital stay. The median Hunt and Hess score for patients included was 2 (range 1–4).

Overall, the SAH patients exhibited a consistent increase in their maximum daily pain score, rising from a median of 5 on hospital day 1 to 8 on hospital day 7 (Fig. 1). This increase appeared independent of the type or amount of pain medication given. Patients with early vasospasm had a higher overall median daily pain score than did patients without vasospasm (early vasospasm pain score 8 vs. no vasospasm pain score 6, $p = 0.0002$). These data suggest that the headache associated with aneurysmal SAH is severe and increases in severity as the patient progresses through the putative vasospasm window. In addition, the presence of early vasospasm may be significantly associated with the worsening of headache during this time period. Only one patient (1/14) who experienced early vasospasm had a mild headache (maximum pain score ≤ 4), whereas 35.5% (27/76) of patients with severe headache (maximum pain score ≥ 8) had early vasospasm ($p = 0.035$). Mean TCD values also increased similarly to pain score during this period (Fig. 2). Overall, mean TCD values were not significantly different (either mean measurements or Lindegaard ratio) in patients with mild vs severe headache.

The primary analgesic medication given to patients in this cohort of patients was Fioricet (Table 2). Nearly every patient in this cohort (87%) received at least one dose of Fioricet during the first 7 days of admission. The mean number of tablets of Fioricet given per day increased from 1.6 (SD 2.1) on hospital day 1 to a peak of 5.9 (SD 4.1) on hospital day 5. While some patients required no analgesic medications on a given day, over 32% of the patients required a mean of > 5 Fioricet tablets per day (including 47% of the patients who exhibited early vasospasm). Overall, patients with no vasospasm received comparatively less (4.3 tablets) Fioricet per day compared to patients with early vasospasm, though the difference was not statistically significant (5.5 tablets per day, $p = 0.055$). Patients with early vasospasm also tended to receive opioid agents slightly more than patients without vasospasm, although this was not statistically significant (8.2 mg morphine equivalents vs 5.4 mg morphine equivalents, $p = 0.056$). Other analgesics were used for headache pain including morphine, oral opioid agents, and NSAIDs such as ibuprofen and ketorolac (Table 2). Patients with early vasospasm tended to require more pain medications, with Fioricet and ketorolac being used significantly more in the early vasospasm group. Most of these agents aside from Fioricet and acetaminophen were used sparingly and none of the agents were associated with an improvement in pain score overall. As the number of doses of Fioricet or other analgesics increased, the pain scores also increased, suggesting that the headache is typically treatment-refractory and/or the medications being used to treat the headache are largely ineffective.

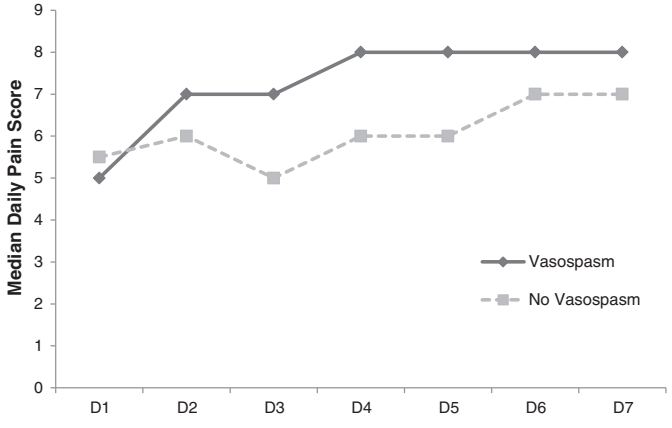

Fig. 2. Daily headache pain scores in patients with and without vasospasm.

Table 2
Analgesics for SAH headache[a].

	Total (n=108)	Patients with vasospasm who received specific therapy (n=34)	Patients with no vasospasm who received specific therapy (n=74)	P-value
Fioricet	94 (87%)	33 (97.1%)	61 (82.4%)	0.036
Acetaminophen	54 (50%)	21 (61.8%)	33 (44.6%)	0.097
Ibuprofen	10 (9.3%)	2 (5.9%)	8 (10.8%)	0.411
Ketorolac	18 (16.7%)	10 (29.4%)	8 (10.8%)	0.016
Total morphine equivalents[b]	87 (80.5%)	26 (76.5%)	61 (82.4%)	0.467
Dexamethasone	26 (24.1%)	10 (29.4%)	16 (21.6%)	0.379

[a] All data for medications include N (%) of patients who received specific agent.
[b] Includes equipotent doses of oral opioids (hydrocodone, oxycodone, and codeine) and IV morphine.

The serum magnesium concentration was also examined for each patient. Nearly all patients (94%) had at least one magnesium concentration obtained during the first 7 days of their hospital stay (though most patients had magnesium monitored daily). The mean magnesium concentration was 2 mg/dl (SD 0.36) and was not different between patients who had early vasospasm vs no vasospasm. Magnesium concentrations >2 mg/dl were not associated with lower pain scores or improvements in pain scores.

A multivariate analysis was also performed in order to determine any relationship with vasospasm and patient factors (Table 3). In the univariate analysis, age, amount of Fioricet use, and TCD values were positively associated with the occurrence of early clinical vasospasm. However, the results of the multivariate analysis did not demonstrate a significant association with age, Fioricet use or TCD values with early clinical vasospasm.

Discussion

This study of headache in the first 7 days after aneurysmal SAH demonstrates that headache is common, even days after the sentinel hemorrhage. Patients who develop cerebral vasospasm early after SAH have a significantly higher pain score related to their headache than do patients without vasospasm. Additionally, patients who complained of a severe headache (defined as a pain score $\geq 8/10$) more frequently developed early vasospasm than did patients who complained of a mild headache (defined as a pain score $\leq 4/10$). Unfortunately, a wide variety of agents was used in our cohort with limited success. This is the first study to specifically describe the severity of headache after aneurysmal SAH.

Table 3
Multivariate logistic regression predicting the outcome of clinical vasospasm.

Variable	Parameter Estimate	Odds ratio	95% CI for OR	P-value
Age	−0.034	0.97	0.93–1.00	0.08
Hunt and Hess Score[a]	−0.340	0.51	0.19–1.37	0.2
Average Fioricet Dose[b]	0.096	1.10	0.96–1.27	0.2

[a] Hunt and Hess Score was dichotomized as 1+2 vs 3+4. Hunt and Hess Score of 3+4 was used as reference in multivariate logistic regression.
[b] Mean dose for Fioricet was expressed as tablets per day.

The data in the present study suggest that headache pain after SAH is significant and that it increases in intensity during the first 7 days after ictus. While the mechanism of headache after SAH is not well described, it is plausible that many of the factors that contribute to the development of vasospasm may also lead to headache. Certainly, the chemical irritation of blood on the meninges and in the subarachnoid space is thought to cause pain. In addition, infiltration of immune cells, immune activation, and inflammatory cytokines likely also contribute to the pain associated with headache [14]. It may also be possible that alterations in brain perfusion associated with vasospasm may factor in the intensity of the headache. Very little data are available to directly corroborate these mechanisms, so much research in this area is needed before clinicians have a better understanding of the disease process.

The use of Fioricet as the primary analgesic in this cohort did not appear to be effective. Despite an increase in daily usage throughout most of the first 7 days after ictus, the median daily pain scores continued to rise. Concerns about the safety of using this combination agent were not entirely disproven. A univariate analysis of factors associated with vasospasm suggested that daily Fioricet dose was associated with the development of vasospasm. However, the multivariate analysis, when correcting for severity of SAH and age, did not show a significant association. It is difficult to discern whether an increased dose of Fioricet promoted the development of vasospasm or if increasing vasospasm was associated with worsening headache (and hence the need for more analgesia). The pharmacology of caffeine and the impact on cerebral vasoconstriction still merit further study to ensure that clinicians are not administering a deleterious agent in this clinical context. In addition, the subtle effects of a long-acting barbiturate like butalbital are difficult to evaluate in a retrospective study design. It is unknown whether receipt of this agent had an impact on patient wakefulness or neurologic exam. Certainly, avoiding CNS depressants in patients where small, insidious changes in neurologic exam may herald significant morbidity continues to be advisable. We also did not detect a significant occurrence of acetaminophen overdosing, although it is generally our practice to be vigilant about the amount of acetaminophen available to be given on a daily basis in these patients. Of the 729 patient days evaluated, there were 9 instances (1.2%) where a patient received 4 g of acetaminophen or more (maximum in one day was 4575 mg). No liver toxicity was noted in any of the patients studied. Clearly Fioricet, in addition to others, is not a panacea for the treatment of peri-SAH headaches.

There are several limitations to this study and the interpretation of the data. First, as a retrospective study, we are missing many of the qualitative aspects of the pain score and the patient experience after SAH. In the future, prospective studies in this area should include more qualitative assessment of the patient's pain and comfort. Second, analgesics were not used in a protocolized manner. While this is quite reflective of a 'real-life' scenario, it also makes evaluation of the efficacy of these agents difficult. It is quite possible that a systematic method of treating headache in these patients (escalating doses of medications, strategic combinations of agents which might synergize in effect, etc.) may be more beneficial than a variable, inconsistent practice. Third, for patients who had limited consciousness, there was not an established nursing protocol for headache assessment and treatment. Intensive care nurses often use physiological and behavioral cues to evaluate pain in these cases (tachycardia, grimacing, agitation, etc.), but this is challenging to quantify on a 10-point analog scale. Therefore, we are limited in evaluating these data in the context of severe SAH patients or those with declining GCS. Fourth, we did not include the development of hydrocephalus in our analysis of headache pain. However, we typically employ CSF diversion with a ventriculostomy to attenuate hydrocephalus in these clinical situations, so we do not believe this factored greatly into our results. Finally, acceptable pain levels are different for each unique patient (and often different for a given patient on different days). We did not evaluate the pain score in light of the patient's stated acceptable pain score, so it is possible that some patients had a relatively high pain score, but did not consider it clinically significant. However, the incremental trend we observed in pain score suggests that pain did worsen considerably in the cohort overall.

Conclusions

We evaluated headache pain scores in patients within 7 days of their aneurysmal SAH. Overall, pain scores increase on a daily basis after SAH, rising from a median of 5 on day 1 to 8 on day 5. Patients who developed cerebral vasospasm appeared to have a more severe headache than those patients who did not develop vasospasm. Fioricet was the primary analgesic administered for headache in this cohort. Our data suggest that this agent was largely ineffective in treating headache in these patients. Furthermore, a univariate analysis suggested that Fioricet may be associated with early vasospasm, although this was not corroborated by the multivariate analysis correcting for SAH severity and age. This is the first descriptive report of the course and severity of headache after aneurysmal SAH. It seems clear that this is a significant problem for patients after ictus and that our current treatment strategies are not effective at this point. Prospective evaluation of treatment strategies aimed at providing adequate analgesia while not confounding neurologic exam or contributing to other morbidity after SAH is needed.

Conflicts of interest statement

None of the authors have any potential or actual conflicts of interest in relation to this manuscript.

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