Inadequacy of Headache Management After Subarachnoid Hemorrhage

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Background Headache profoundly affects management of spontaneous subarachnoid hemorrhage but is poorly characterized.

Objective To characterize headache after spontaneous subarachnoid hemorrhage.

Methods Medical records of patients with Hunt and Hess grades I-III subarachnoid hemorrhage admitted from 2011 to 2013 were reviewed. Demographics, clinical and radiographic features, medications, and pain scores were recorded through day 14 after hemorrhage. Headache pain was characterized on the basis of a numeric rating scale and analgesic use. Severe headache was defined as 2 or more days with maximum pain scores of 8 or greater or need for 3 or more different analgesics for 2 or more days. Univariate and multivariable models were used to analyze factors associated with severe headache.

Results Of the 77 patients in the sample, 57% were women; median age was 57 years. Severe headache (73% overall) was associated nonlinearly with Hunt and Hess grade: grade I, 58%; grade II, 88%; and grade III, 56% (P = .01), and with Hijdra score: score 0-10, 56%; score 11-20, 86%; score 21-30, 76% (P = .03). By univariate analysis, patients with low Hijdra scores were less likely to have severe headache (27% vs 57%; P = .02). In a multivariable model, younger age and higher Hijdra score tended to be associated with severe headache.

Conclusions Headache after spontaneous subarachnoid hemorrhage was often severe, necessitating multiple opioid and nonopioid analgesics. Many patients reported persistent headache and inadequate pain control. (American Journal of Critical Care. 2016;25:136-143)
Aneurysmal subarachnoid hemorrhage (SAH) occurs at a rate of 3 to 25 cases per 100,000 population annually, typically requires intensive medical and neurosurgical care, and may result in a fatal or devastating neurological outcome.1 The ictal headache of SAH is often described as the “worst headache of a patient’s life,” beginning with the “thunderclap” and followed by a chronic headache that may persist for weeks, months, or even years after the hemorrhage.2,4 In the initial phase of hospitalization after aneurysmal rupture, headache and its management cloud the neurological assessment, may interfere with the important diagnosis of vasospasm, and may be a risk factor for delirium.7-11 Headache that persists in the subacute and chronic phases after SAH is poorly understood and inadequately characterized.

Despite the high prevalence, associated morbidity, and effects on quality of life of SAH-associated headache, epidemiological studies of its timing, severity, characteristics, and usual treatments are lacking. In the MASH-2 trial12,13 (magnesium in aneurysmal SAH), patients with higher magnesium levels (> 1.0 mmol/L) had slightly lower mean pain scores (4.1 vs 4.9) on a numerical rating scale and lower use of analgesics compared with patients with normal levels of magnesium (≤ 1.0 mmol/L). In another study,2 among patients with no angiographic evidence of SAH, 75% experienced severe headache during their inpatient stay, and 25% experienced persistent headache at a mean follow-up of more than 24 months after discharge. The results of a prospective study14 published in 2013 indicated that headache was the second-leading cause for 30-day hospital readmission after SAH. Long-term follow-up data indicate that headache may persist after SAH for 2 to 9 years.2-6 Review articles typically mention headache after SAH without making specific recommendations for managing the headache after the initial episode.

Follow-up data indicate that headache after subarachnoid hemorrhage may last for 2 to 9 years.

Methods

Patients

Consecutive patients were 18 years or older and admitted from January 1, 2011, to March 1, 2013, with nontraumatic SAH of Hunt and Hess grades I, II, or III. Patients were characterized according to the worst Hunt and Hess grade in the initial 24 hours after admission. Patients with Hunt and Hess grades IV and V and those requiring intubation and sedation for more than 24 hours during...
the study period were excluded because the intensity of their headaches could not be assessed.

SAH Protocol
Patients with SAH were admitted to a dedicated neuroscience intensive care unit. Symptomatic hydrocephalus was treated with external ventricular drainage. All patients had digital subtraction angiography unless computed tomography angiography showed a culprit aneurysm that required surgery. Aneurysms were urgently secured by endovascular coiling unless surgical clipping was technically necessary. The SAH protocol included standard enteral administration of nimodipine 60 mg every 4 hours; simvastatin or atorvastatin 40 mg/d, intravenous infusion of 0.9% sodium chloride solution at 100 to 150 mL/h, and maintenance of the serum magnesium level at more than 2.3 mg/dL. Transdermal nicotine replacement therapy was provided to smokers of more than 0.5 packs per day.

Transcranial Doppler imaging was performed daily or every other day at the managing physician’s discretion, and a neurological examination was performed every 1 to 2 hours by nurses or physicians. All patients were initially treated in a dedicated neuroscience intensive care unit; a few patients with Hunt and Hess grade I to II SAH deemed at low risk for vasospasm were subsequently managed in a neurological intermediate care unit. Results of headache and neurological examinations were recorded by nursing staff as described in the following material.

Data Points and Definitions
Data collected included age; weight; sex; hospital course (date of SAH, admission date, hospital discharge date, in-hospital mortality, discharge disposition); relevant medical and social history (alcohol or tobacco use, headache or migraine, medications used before admission to treat preexisting headache); clinical features (location of aneurysm, maximum daily temperature, development of elevated intracranial pressure [defined as sustained pressure > 20 mm Hg for 2 hours, requiring medication or hyperventilation], hydrocephalus, seizure, meningitis, ventriculitis); Hunt and Hess grade (worst grade I-V in initial 24 hours after admission); Hijdra scores (measure of blood volume in the subarachnoid space; range, 0-30); interventions performed (coiling, clipping, external ventricular drain, shunt, lumbar puncture); radiographic features (transcranial Doppler imaging and angiographic findings); pain scores recorded; and medications used for headache pain.

Severe headache was defined on the basis of severity or refractory nature.

Analgesic agents, administration times, and doses were obtained and recorded by review of an electronic medication administration record. Total daily dose of each medication was calculated for each day of hospitalization after hemorrhage during the study interval. Each day of the study period was considered the 24-hour period from midnight to midnight, resulting in partial days at the beginning or the end of the study period, depending on times of admission and discharge. Severity of headache was determined via pain scores reported by patients using a numerical rating scale (scores 0-10, with zero meaning no pain and 10 meaning worst pain imaginable). Electronic documentation of pain scores included site of pain; only pain scores related to headache were included. All documented pain scores obtained before administration of medication were recorded; data analysis included daily maximum and median scores. Pain scores obtained after administration of medication were not consistently recorded and therefore were excluded from calculations of maximum and median pain scores. Hunt and Hess grades (I-III) and Hijdra scores (0-30) were calculated by neurointensivist physicians by using the initial head computed tomography scan. The outcome severe headache was defined on the basis of severity (≥ 2 days with maximum pain scores ≥ 8) or refractory nature (requiring ≥ 3 different analgesics on ≥ 2 days). Radiographic evidence of vasospasm was defined as transcranial Doppler velocities of more than 120 cm/s at the middle or anterior cerebral artery in conjunction with a Lindegaard ratio of 3.0 or greater. Discharge medications were determined by reviewing patient discharge summaries in the electronic medical record.

Statistical Methods
Daily drug dosing data for each patient were recorded as delivered doses of various types of drugs during the study interval. The study interval consisted of the number of days of hospitalization and was capped at day 14 after hemorrhage. In order to calculate a uniform metric to quantify the total daily opioid dose per patient per day, the recorded doses of the various opioid agents were converted to their intravenous morphine equivalent by using the appropriate conversion factors. The total resultant dosage was calculated as the sum of all converted doses for each patient for each day in the study interval and was presented as morphine-equivalent dose. Maximum and median daily opioid dosage was determined by examining these aggregated daily data.

Pain data were recorded as responses on a scale from 0 to 10. Plots of the mean daily maximum and median pain scores were developed. The data were categorized into cohorts according to Hunt and Hess.
Hess grade (I, II, III), volume of blood in subarachnoid space (Hijdra score 0-10, 11-20, 21-30), and by severe headache or no severe headache. Mean intercohort differences were compared by using $\chi^2$ tests. Finally, clinical variables considered most likely to be related to headache, including age, sex, Hunt and Hess grade, Hijdra score, radiographic evidence of vasospasm, aneurysmal etiology, hydrocephalus, and presence of an external ventricular drain were used in a stepwise logistic regression model against the occurrence of severe headache. SAS, version 9.3, software (SAS Institute) was used for analyses. A cutoff of $P$ less than .30 was established for inclusion in the model; variables that did not meet this criterion were removed.

**Results**

Of the 126 patients screened, 49 were excluded, resulting in a sample size of 77 patients (Figure 1). The Table gives patients’ demographics, clinical variables considered most likely to be related to headache, and disposition.

**Figure 1** Flow chart of selection of patients.

<table>
<thead>
<tr>
<th>Table Characteristics of patients in the study</th>
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<tbody>
<tr>
<td>Characteristic$^a$</td>
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<td></td>
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<tr>
<td>Age, median (IQR), y</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>Weight, median (IQR), kg</td>
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<td>Active tobacco use</td>
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<tr>
<td>History of headache/migraine</td>
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<tr>
<td>Hunt and Hess grade</td>
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<td>I</td>
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<td>II</td>
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<td>11-20</td>
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<tr>
<td>21-30</td>
</tr>
<tr>
<td>External ventricular drainage</td>
</tr>
<tr>
<td>Aneurysm identified$^b$</td>
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<tr>
<td>Hydrocephalus</td>
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<tr>
<td>Radiographic evidence of vasospasm$^c$</td>
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<tr>
<td>Disposition</td>
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<tr>
<td>Discharged to home$^b$</td>
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<tr>
<td>Discharged to rehabilitation center$^b$</td>
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<tr>
<td>Discharged to skilled nursing facility$^b$</td>
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<tr>
<td>Died before discharge</td>
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</tbody>
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Abbreviation: IQR, interquartile range.

$^a$ Values in second, third, and fourth columns are number (percentage) of patients unless otherwise indicated in the first column.

$^b$ Data missing for 1 patient with no severe headache.

$^c$ Data missing for 2 patients with severe headache and 1 patient with no severe headache.
Headache was common, with high pain scores throughout the hospitalization and minimal decreases during the study period. Maximum and median pain scores are shown in Figure 2: the decrease in median pain scores between days 0 and 14 after the subarachnoid hemorrhage was only 17%. Figure 3 shows use of medications with analgesic effect during the study period. Of note, some postoperative patients were given dexamethasone to prevent or reduce edema, and distinguishing this use from use to decrease meningeal irritation and headache was impossible. The maximum total daily dose of dexamethasone was 16 mg administered as 4 mg every 6 hours. Only a few patients (5%) completed the 15-day study period without receiving any opioid analgesic. The mean opioid use by hospital day, expressed in intravenous morphine equivalents, is shown in Figure 4. Most study patients (75%) required opioid prescriptions for headache pain when they were discharged from the hospital.

Severe headache was experienced by 11 patients (58%) with Hunt and Hess grade I SAH, by 35 (88%) with grade II, and by 10 (56%) with grade III (P = .01). Similarly, severe headache was experienced by 15 patients (56%) with Hijiira scores of 0 to 10, by 25 (86%) with scores of 11 to 20, and by 16 (76%) with scores of 21 to 30 (P = .03). The distributions, while indicative of association with the underlying process, were not sufficiently linear to be used in determining prediction or causality of headache, as indicated in the subsequent multivariate analyses.

Stepwise logistic regression analysis was used to isolate clinical factors independently associated with severe headache. In the final model, Hijiira score (odds ratio, 1.09; P = .06) and age (odds ratio, 0.95; P = .08) had no significant independent associations with headache. A weak but nonsignificant association was found between severe headache and radiographic evidence of vasospasm (P = .30) or hydrocephalus (P = .32). These variables were dropped from the model on subsequent stepwise elimination by using an inclusion cutoff of P less than .30. Severe headache after SAH was not associated with placement of an external ventricular drain, aneurysmal vs nonaneurysmal SAH, or Hunt and Hess grade.

**Discussion**

Headache after SAH persisted well beyond the initial ictal event. Most patients hospitalized with Hunt and Hess grade I, II, or III SAH (73%) met our criteria for having severe headache during the 15-day study period. Patients often required opioid and nonopioid analgesics; opioid usage peaked at a mean daily morphine-equivalent dose of 18 mg intravenously on days 4 to 5 after the hemorrhage.
Both dexamethasone and butalbital/acetaminophen/caffeine were often administered (Figure 3). Patients with less subarachnoid blood were less likely than those with more blood to experience severe headache ($P = .02$), although the finding was not significant in the multivariable model ($P = .06$). Finally, we noted a trend toward association of severe headache and younger age. Patients reported inadequate pain control during hospitalization, and most required opioid prescriptions at the time of discharge from the hospital.

Previous descriptions of persistent headache in patients with SAH are limited. In 1 study,2 rates of severe headache during an inpatient stay were similar to the rates in our study; 74% to 81% of SAH patients with no angiographic evidence of aneurysm experienced severe headaches. In follow-up after discharge, 23% of patients had depression and headache at a mean of 28 months (range, 2-84 months). In a study of long-term neurological and psychological outcomes after SAH, 16.5% of patients reported frequent or severe headache 4 to 7 years after SAH. Headaches were significantly correlated with difficulty in nighttime sleep ($r = 0.28; P = .001$). In a study published in 1998, Linn et al27 interviewed SAH survivors and found that all patients with a history of headache rated the SAH headache more severe than usual headaches. In a study of 149 patients with perimesencephalic SAH admitted to University Medical Center Utrecht in the Netherlands, follow-up interviews conducted at a mean of 7.5 (range, 1-23) years after the hemorrhage revealed that 25% of the study patients had headaches, dizziness, fatigue, forgetfulness, and irritability. Finally, investigators in the 610-patient Aneurysm Screening after Treatment for Ruptured Aneurysms (ASTRA) study conducted interviews with patients at a mean of 8.9 years after SAH clipping. Patients widely reported fatigue, headache (12%), and difficulty with concentration.

Our results provide a detailed and comprehensive description of pain severity and headache treatments used in the acute phase of SAH management and indicate opportunities for improved patient care. Although our research was performed at a single center and is subject to biases associated with the study design, we think our findings provide a valuable snapshot of patient care and reveal a pattern of inadequate pain management.

Our study has weaknesses. Because of the retrospective design, omissions and inaccuracies in data collection and preservation are possible. The number of patients in our sample was modest. Nursing records were inconsistent, especially in documentation of pain after administration of analgesic medication. Pain assessment was conducted by several different nurses during the study period. The patient admission and discharge time could have resulted in underreported use of analgesics for patients with partial admission days. Owing to the limitations of the pain scale normally used in patients with SAH, we developed a new definition of severe headache by using a combination of patient-reported severity, persistence of pain, and analgesic requirements. The duration of at least 2 days was included to ensure headache pain was present beyond the initial thunderclap headache. The pain score threshold of 8 on a numerical rating scale was determined via our informal survey of critical care nurses, who determined that a pain score of 8 or greater indicated severe headache. The threshold of 3 analgesic medications was determined by our informal survey of critical care pharmacists.

Our definition of severe headache has not been used before and should be reevaluated prospectively. Our definition may not be appropriate for detecting severe headache in patients who require high doses of 1 or 2 medications. Furthermore, although a numerical rating scale is widely used in hospitals around the world to describe pain levels, the scale may not be appropriate for patients with SAH because of the patients’ variable levels of consciousness, which might affect the ability to verbalize and rate discomfort. This variability may be the reason that fewer pain scores were reported and documented.
among patients with Hunt and Hess grade III SAH and among patients with the highest amount of blood in the subarachnoid space (Hijdra scores > 21), who had somnolence. The need for a pain scale designed specifically to rate pain in SAH patients is apparent, and these limitations weaken our analysis.

Certain medications used to manage headache pain in our study warrant discussion. Dexamethasone was given to many of patients, at a maximum total daily dose of 16 mg. High-dose corticosteroids are not recommended for patients with acute SAH,16,17 as indicated by the results of the Corticosteroid Randomisation After Significant Head Injury (CRASH) trial,29 which showed that use of high doses of methylprednisolone in patients with head injury was associated with an increased risk of death. The dexamethasone dose used during our study is commonly used for management of cerebral vasogenic edema or meningeal irritation and is equivalent to approximately 85 mg methylprednisolone daily, which is less than 1% of the greater than 10000 mg/d dose used in the CRASH trial. Additionally, the majority of patients received opioids during our study interval, often at high doses. Owing to their propensity to cause sedation and cloud the neurological examination, opioids are not ideal analgesics for patients with SAH. However, opioids were often used because of the severity of pain and lack of success with alternative, less sedating agents. Nonanalgesic medications with sedating properties and their doses were not recorded.

We found a nonlinear association of SAH severity (determined by Hunt and Hess grade) and volume of subarachnoid blood (determined by Hijdra score) with severe headache. Patients with Hunt and Hess grade II and Hijdra scores of 11 to 20 had the highest incidence of severe headache. The nonlinearity of this association of headache severity with SAH severity is not surprising because higher grade SAH causes obtundation and coma, most likely resulting in underreporting of pain, whereas patients with lower grade SAH may experience less meningeal irritation. The standard Hunt and Hess grading definitions were problematic, because the scale includes headache in its definition; for this reason, the World Federation of Neurological Surgeons grading system for SAH may be more appropriate for further research on SAH-associated headache. Furthermore, the lack of association noted between vasospasm and headache could be due to the small number of patients, the insensitivity of transcranial Doppler imaging to show evidence of vasospasm,30 or to a true lack of association. Finally, we could not distinguish the use of dexamethasone for headache from its use for edema.

Despite these weaknesses, our study is the first in which headache after SAH was quantified, and our results suggest many important topics for prospective study: optimal therapies for headache after SAH, how headaches after SAH should be rated, whether headache control is independently associated with functional and cognitive outcomes, what agents provide the best control of headache after SAH, and whether superior headache control might improve patient-centered outcomes such as quality of life.

Conclusions

Headache after SAH causes marked suffering that persists at a high level of severity for at least 2 weeks and is associated with the volume of blood apparent in the subarachnoid space on the initial head computed tomography. SAH-related headache often requires high doses of opioid analgesics and other sedating and potentially deliriogenic medications, which provide incomplete and often inadequate pain relief. Headache after SAH is therefore a major cause of suffering and morbidity and deserves intensified research to develop novel and effective therapies.

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FINANCIAL DISCLOSURES

None reported.

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