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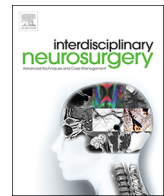
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Research Article

Treatment of headache in aneurysmal subarachnoid hemorrhage: Multimodal approach

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ABSTRACT

Sudden severe headache is a cardinal symptom and the most common complaint amongst patients presenting with aneurysmal subarachnoid hemorrhage. The multifactorial etiology of these headaches makes pharmacotherapy problematic. Current aneurysmal subarachnoid hemorrhage guidelines have limited or no recommendations for headache treatment. Our institution utilizes a multimodal pharmacotherapy protocol in the management of aneurysmal subarachnoid hemorrhage headache. The purpose of this study was to evaluate the efficacy of the current aneurysmal subarachnoid hemorrhage headache treatment approach at our institution. This was a retrospective cohort study of patients presenting with aneurysmal subarachnoid hemorrhage. A multimodal aneurysmal subarachnoid hemorrhage headache treatment protocol was implemented in February 2014. After an eight-month washout period, patients treated between September 2014 and November 2017 represented the study cohort. Data collected included severity of aneurysmal subarachnoid hemorrhage and headache, interventions to secure the aneurysm, pain score response related to specific analgesic administered, and discharge status. Multivariate analysis and linear regression were used to identify predictors of treatment efficacy. A total of 249 patients were identified in the study cohort. The majority of patients were female (61.4%) with a median age of 54 years ($\pm$ 12.5), median Hunt and Hess score of 2 (interquartile range 2–3), and mean length of hospitalization of 15.2 days. Magnesium infusion had the largest reduction in mean pain score compared to baseline pain score (-0.75; p = 0.0002). In this retrospective cohort study involving patients presenting with headache secondary to aneurysmal subarachnoid hemorrhage, no agent resulted in a clinically significant improvement on headache pain scores.

1. Introduction

Sudden severe headache is a common complication of aneurysmal subarachnoid hemorrhage (aSAH) [1,2]. The cause of headaches related to aSAH is likely multifactorial, with local inflammation of cerebral arteries, chemical irritation of the meninges by the blood in the subarachnoid space, and intracranial pressure changes [3,4]. Over time, red blood cells (RBCs) are degraded to oxyhemoglobin, inhibiting nitric oxide and stimulating endothelin-1. In addition, release of reactive oxygen species and free iron, as well as production of vasoactive compounds, leads to oxidative damage and cerebral artery constriction. This damage induces secondary inflammatory states and neuronal excitatory activity through calcium influx and *N*-methyl-D-aspartate (NMDA) receptors, thus contributing to cerebral vasospasm and likely exacerbating severe headache [5]. Recent evidence also suggests there may be a neuropathic component to these headaches as well [6].

Overall, the complicated multifactorial etiology of these headaches makes targeted pharmacotherapy problematic. Current aSAH guidelines have limited or no recommendations for headache treatment [7,8]. Use of common agents for headaches such as non-steroidal anti-inflammatory agents (NSAIDs) and opioid analgesics are limited in patients with aSAH by their respective risks. NSAIDs have the potential to increase the risk of bleeding after aSAH, while opioid sedative effects have the potential to obscure the neurologic exam in patients who require close monitoring for the detection of cerebral vasospasm. In addition, agents typically used for migraine (such as acetaminophen/butalbital/caffeine or triptans) may cause cerebral vasoconstriction, which may be deleterious in patients at risk of cerebral vasospasm [9]. Reports of success with magnesium and gabapentin have been published, but are not definitive given the study design and small sample size [5,7,9].

Due to the complicated multifactorial etiology and difficulty

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                    ┌─────────────────────────────┐
                    │      Acetaminophen          │
                    │   650 mg PO every 4 hours   │
                    │    for maximum 4 grams/day  │
                    └─────────────────────────────┘
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Acetaminophen
650 mg PO every 4 hours for maximum 4 grams/day

Secured Aneurysm

Unsecured Aneurysm

Ketorolac
30 mg IV every 6 hours for maxim m 5 days, OR
Ibuprofen
600 mg PO every 6 hours

Codeine
30 – 60 mg PO every 4 hours PLUS
Acetaminophen
650 mg PO every 4 hours for maximum 4 grams/day

Codeine
30 – 60 mg PO every 4 hours PLUS
Acetaminophen
650 mg PO every 4 hours for maximum 4 grams/day

Magnesium sulfate
4 grams IV every 4 hours until > 2 gm/dL

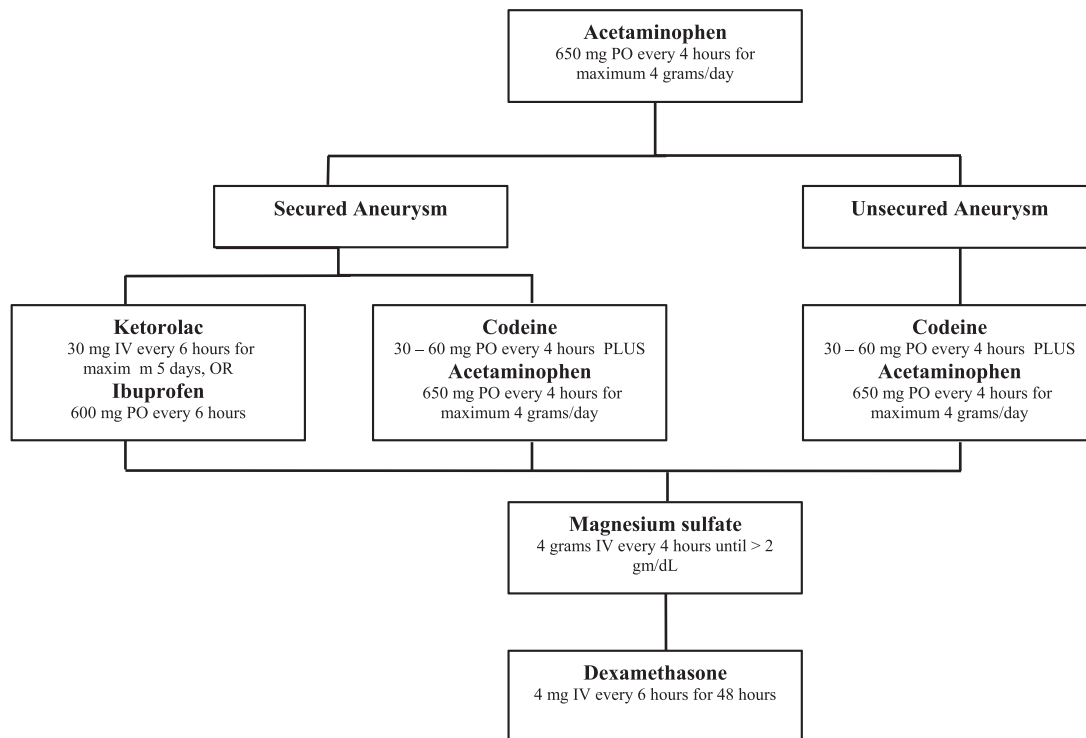**Dexamethasone**
4 mg IV every 6 hours for 48 hours

Fig. 1. Acetaminophen is used first for headache pain. For patients with secured aneurysms, nurses may use NSAIDs or codeine products as second tier therapy if headache pain persists. For patients with unsecured aneurysms (or those that have no angiographic evidence of aneurysms), only codeine products are available as second tier therapy. If second tier therapy fails to improve headache pain, the nurse supplements magnesium intravenously to a serum concentration of > 2gm/dL. If magnesium supplementation does not improve headache pain, a short course of dexamethasone is initiated.

controlling headache pain our institution established a multimodal protocol for the management of aSAH headache incorporating various pharmacologic agents with different mechanisms of action in sequence. The purpose of this study was to evaluate the efficacy of current aSAH headache treatment at our institution. The hypothesis of this study was that none of the agents in the current protocol have a significant impact on headache scores.

2. Materials and methods

This study was a retrospective cohort study of adult patients presenting to University of Kentucky HealthCare (UKHC) who were admitted with aSAH. The University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust was used to identify patients with the diagnosis codes for aSAH between September 2014 and November 2017. The multimodal aSAH headache treatment protocol (Fig. 1), was implemented in February 2014. After an eight-month washout period, patients treated between September 2014 and November 2017 represented the study cohort. This cohort included patients ≥ 18 years of age, who received an analgesic for the treatment of aSAH-associated headache, and had a hospital length of stay ≥ 3 days. Patients were excluded if the subarachnoid hemorrhage was inflicted by trauma, inadequate medication administration records or incomplete medical records were present, or if they presented with Hunt and Hess Grade V aSAH. Local institutional review board approval was obtained via expedited review.

The study site is a Joint Commission accredited comprehensive stroke center and a regional referral center for the management of various types of stroke, particularly aSAH. Treatment of patients with aSAH is largely reflective of guideline recommendations [7]. Aneurysm embolization or clipping is typically performed within the first 24–48 h after presentation when possible. Patients are routinely observed in the intensive care unit for the first 7–14 days, depending on aSAH severity and other clinical factors. Patients are prescribed nimodipine 60 mg

orally every 4 h. Euvolemia and normonatremia are targeted. Headache management is typically followed by protocol (Fig. 1) for patients who are oriented and able to interact with the nurse. Visual and physiologic cues of pain are used in patients who are less responsive where the pain score cannot be specifically enumerated. A computerized order set was entered for each patient with the algorithm approach from Fig. 1. We did not evaluate adherence to the algorithm in this study.

The primary outcome of this study was to evaluate the efficacy of various medications used for headache, measured as the change in patient reported pain scores two hours after medication administration. Each patient's pain scores (on a 0–10 point analog scale) were routinely monitored by nursing staff to assess the efficacy of protocol-guided analgesics before and after medication administration.

Data points collected included patient demographics such as age and smoking history, pain scores through seven days, total number of analgesic doses per day through seven days, aSAH characteristics (severity and method of aneurysm intervention), and length of stay. Other data included daily maximum and average patient scores through admission, total number of analgesic doses per day through admission, pain score response related to specific analgesic administered, and need for rescue therapy (administration of an opioid excluding codeine). Multivariate analysis and linear regression were used to identify treatment efficacy for each analgesic. Alpha was set at $p < 0.05$. All statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 301 patients were identified within the designated time period. Of those patients, 52 patients were excluded due to presentation with Hunt and Hess Grade V aSAH. The demographics for the study cohort are outlined in Table 1. The majority of patients were female (61.4%) with a mean age of 54 years (± 12.5), and a median Hunt and Hess score of 2 (interquartile range 2–3). The mean length of

Table 1
Patient demographics.

	Study Cohort (n = 249)
Age (years) Mean (S.D.)	54.0 (12.5)
Gender (n, % female)	153 (61.4)
Weight (kg) Mean (S.D.)	85.1 (24.8)
History of tobacco use (n, %)	122 (50.8)
Hospital length of stay (days) Mean (S.D.)	15.2 (11.8)
Presenting Hunt & Hess Score Median (IQR)	2 (2–3)
Method of aneurysm intervention	
Coiling (n, %)	161 (64.6)
Clipping (n, %)	9 (3.6)
Angio-negative/non-aneurysmal (n, %)	79 (31.7)

hospitalization was 15.2 days ± 11.8 and more than half of the patients reported previous or current tobacco use (50.8%). The daily maximum pain score was typically between 5 and 7 (on a scale of 0–10) for the study period (Fig. 2).

The details of the rate of use of each analgesic is described in Table 2. Nearly all patients in the study cohort received acetaminophen (98.8%) and magnesium (95.6%). Codeine (59.8%), ketorolac (28.1%), and ibuprofen (27.7%) were also frequently used. NSAIDs (ketorolac and ibuprofen) were used only in patients who underwent aneurysm embolization or clipping, in order to reduce the risk of re-bleeding. Oxycodone (15.3%) was used infrequently and typically as a last-line option. Other intravenous opioid agents were used sparingly. Analgesics that were co-administered were not assessed. Gabapentin (11.6%) was typically used as continuation of home therapy and rarely as a last-line option.

When comparing pain score reduction before and after specific analgesic administration in the study cohort, several analgesics exhibited a significant pain score reduction within 2 h of administration (Table 2, Fig. 3). Magnesium had the largest reduction in mean pain score (-0.75; $p = 0.0002$) followed by acetaminophen/butalbital/caffeine (-0.6354; $p = 0.0003$), ketorolac (-0.60; $=0.0002$), and acetaminophen plus codeine (-0.57; $p = < 0.001$). Oxycodone was the only medication shown to increase the pain score 2 h after administration, however, this was not statistically significant (0.428; $p = 0.089$). Other common protocol options such as acetaminophen, ibuprofen, dexamethasone, gabapentin, and hydrocodone did not demonstrate a significant pain reduction from the baseline pain score.

4. Discussion

In this retrospective cohort study involving patients with headache secondary to aSAH, magnesium had the largest reduction in mean pain score followed by acetaminophen/butalbital/caffeine, ketorolac, and acetaminophen plus codeine. However, none of the agents were associated with a clinically significant change in pain scores. Despite using a multi-modal approach to pain management, patients with aSAH appear to have treatment refractory headache which does not respond well to pharmacotherapy, which corroborates with our first report of treatment of headache in his population, as well as the experiences of other similar centers [9,10].

While numerous options are available for analgesia in patients with aSAH-associated headache, nearly all have aspects that limit their use in this patient population. Acetaminophen was commonly used in the current cohort with little efficacy. Hepatic injury with doses greater than 3-4gm/day limits the dosing of acetaminophen in patients who do not have an adequate therapeutic response. Acetaminophen/butalbital/caffeine is commonly associated with rebound headache upon discontinuation. In addition, a previous univariate analysis suggested that acetaminophen/butalbital/caffeine may be associated with early vasospasm in patients with aSAH, although this was not corroborated by the multivariate analysis correcting for aSAH severity and age [9]. Although acetaminophen/butalbital/caffeine lowered the mean pain score in the current study cohort, the potential risk of early vasospasm and exposure to the long-acting sedative (butalbital) should be considered and alternative pharmacotherapy may be more beneficial. Opioids cause sedation in many patients, which could confound a patient's neurologic exam during the vasospasm risk period, where detection of subtle neurologic changes is of paramount importance.

In patients who undergo aneurysm embolization or clipping, NSAIDs may be useful for headache. Ketorolac was used successfully in the current study cohort, though not with high frequency relative to other protocol options. However, ketorolac is not recommended to be continued for more than 5 days due to hepatic and gastrointestinal adverse effects, which limits the use of this agent to acute, short-term therapy. Ibuprofen may also be used (not concomitantly with ketorolac), but had a less robust response in our cohort.

Opioids are typically reserved for refractory headache due to the potential for sedation and dependence. Codeine plus acetaminophen was used frequently in our patients with some success. It is not routine practice to evaluate pharmacogenetic variability in these patients regarding codeine metabolism, so it is unknown if we used this agent in patients who were hypometabolizers (and would likely have less therapeutic response). Oxycodone was used less frequently and was associated with a worsening of headache in the current cohort. This is likely due to use in patients who have already failed numerous therapies and who are likely to have little to no response to additional therapies as
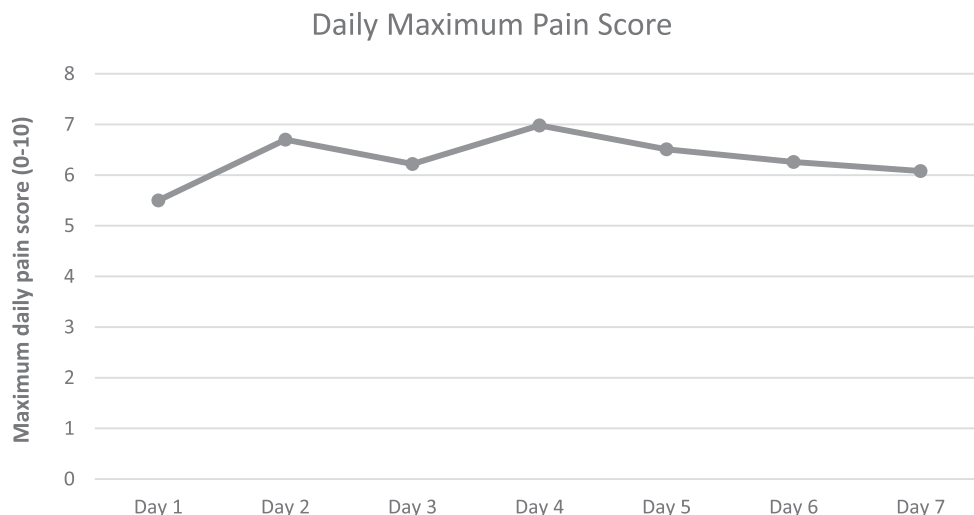

Daily Maximum Pain Score

Fig. 2. The daily maximum pain score was typically between 5 and 7 (on a scale of 0–10) for the study period.

Table 2
Pain score change before and after medication administration.

Medication	Number of patients (%)	Number of Doses	Mean Pain score reduction (S.D.)	P-value
Acetaminophen	246 (98.8%)	519	−0.185 (2.76)	0.1275
Acetaminophen/Codeine	149 (59.8%)	1122	−0.5731 (2.82)	**< 0.0001**
Acetaminophen/Fioricet	81 (32.5%)	288	−0.6354 (2.98)	**0.0003**
Acetaminophen/Hydrocodone	12 (4.8%)	52	−0.3077 (3.00)	0.4630
Ibuprofen	69 (27.7%)	56	−0.4643 (1.91)	0.0738
Ketorolac	70 (28.1%)	241	−0.6058 (2.47)	**0.0002**
Magnesium	238 (95.6%)	185	−0.7568 (2.68)	**0.0002**
Morphine	59 (23.7%)	35	−0.4000 (3.13)	0.4544
Oxycodone	38 (15.3%)	29	0.4828 (1.48)	0.089
Dexamethasone	152 (61%)	308	−0.0390 (2.5863)	0.7917
Gabapentin	29 (11.6%)	100	−0.3500 (2.4552)	0.1571

well.

Several ancillary agents were used in the current cohort with minimal response. Dexamethasone is the primary last-line option in the protocol, thus it was used primarily in refractory cases of headache, which may explain why it was not associated with a significant reduction in pain. Dexamethasone doses were given to patients in the current study for reasons other than headache (eg. stridor), which may have also tempered the effect on change in pain scores. More recently, gabapentinoids have also been promoted as a potential option in aSAH patients, as well as other types of headache [6]. The current cohort infrequently received gabapentin and typically did so as continuation of home therapy (which is our standard practice to continue agents such as this which may have a withdrawal syndrome), so we are unable to make definitive statements on this therapy. Patients that received gabapentin did not have a statistical difference in mean pain reduction after two hours. The issue of tapering gabapentin and how to handle transitions of care issues for aSAH patients, who often suffer from headache months after ictus, is not well-defined [2,6].

Given the single-center retrospective nature of this study, inherent limitations such as the possibility for patient selection bias and co-founding factors may exist. Changes in care over the time period may have impacted outcomes. The subjective nature of pain and the use of patient-reported pain scales, such as 10-point analog scale used in this study, makes inter-patient pain score comparison challenging. Documentation of acceptable pain levels for each patient was

inconsistent and not recorded as a result. To reduce this limitation, this study focused on the change of pain scores, thus reducing inter-patient variability. Patients who experience more pain may be evaluated more frequently by nursing staff, therefore falsely elevating average pain scores. To neutralize this potential for bias, we not only evaluated the change in pain scores after each analgesic, but also considered the maximum pain score for each day. The location and description of pain was not differentiated and other causes of pain other than headache may contribute to the patient's overall pain. However, severe headache is often the most common complaint and is the overriding source of pain in this patient population. Additionally, despite the use of an adequate wash-out time period, we are unable to determine if the aSAH headache treatment algorithm was followed appropriately. It is well-known that headache associated with aSAH can persist for many weeks, so long-term treatment of headache in this population may not be reflected in the present study. Due to lack of documentation, the influence of other factors which may affect headache such as past medical history of headache or migraine, potential for withdrawal of social or recreational drugs, and the impact of anxiety or fear on headache were not able to be analyzed. We were unable to evaluate the impact of aneurysm embolization or clipping on headache [11,12]. Finally, the interaction of the various medications used in combination in the current multi-modal approach may have impacted efficacy. The current analysis was unable to discern if certain combinations or a certain order of therapy would be additive or synergistic for efficacy. Future prospective
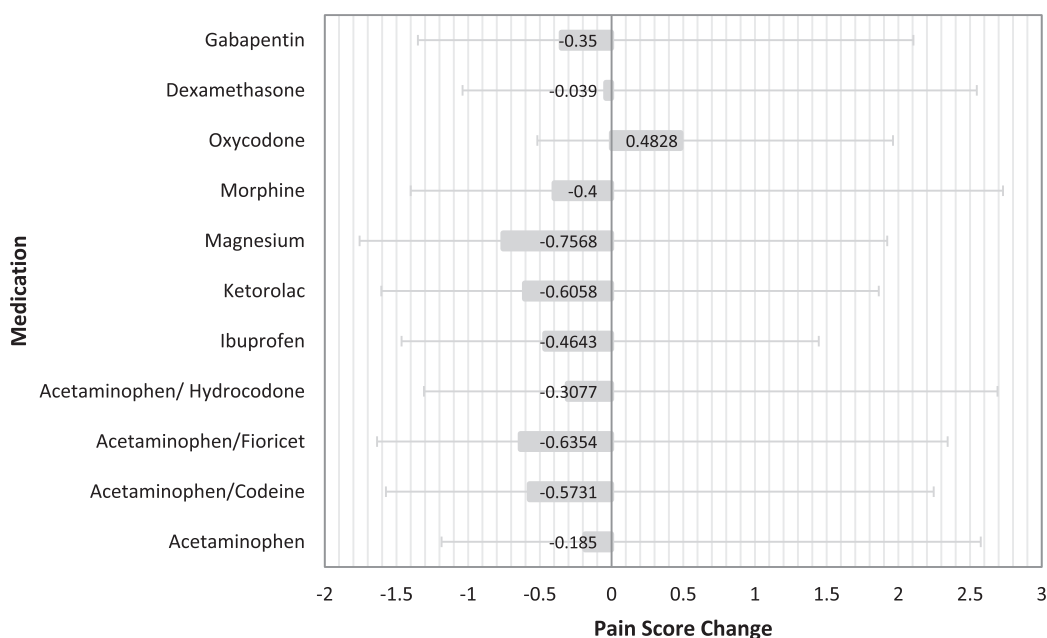

Fig. 3. The mean pain score change within 2 h following medication administration. Magnesium had the largest reduction in mean pain score (−0.75; p = 0.0002). Oxycodone was the only medication to increase the pain score 2 h after administration, however, not shown to be statistically significant (0.428; p = 0.089).

studies are necessary to identify what specific pharmacotherapy agents are most effective to allow for modifications in aSAH headache treatment protocols and the management of these complex patients.

5. Conclusion

In this retrospective cohort study involving patients presenting with headache secondary to aSAH, several agents resulted in a statistically, but not clinically, significant improvement in headache pain scores. Pain scores for patients in the first week after aSAH are elevated and did not change substantially through the week, independent of pharmacotherapy. Clinical and translational research is needed to identify safe pharmacotherapy options that better target the headache associated with aSAH.

CRediT authorship contribution statement

Garrett B. Hile: Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Aaron M. Cook:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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