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ORIGINAL ARTICLE

Safety and Tolerability of Gabapentin for Aneurysmal Subarachnoid Hemorrhage (SAH) Headache and Meningismus

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Abstract
Background Headache after aneurysmal subarachnoid hemorrhage (SAH) is very common and is often described as the "worst headache imaginable." SAH-associated headache can persist for days to weeks and is traditionally treated with narcotics. However, narcotics can have significant adverse effects. We hypothesize that gabapentin (GBP), a non-narcotic neuropathic pain medication, would be safe and tolerable and would reduce narcotic requirements after SAH.
Methods We retrospectively reviewed the clinical, radiographic, and laboratory data of SAH patients at the neuroscience intensive care unit at Mayo Clinic in Jacksonville, Florida, from January 2011 through February 2013. Headache intensity was quantified by a visual analog scale score. Total opioid use per day was tabulated using an intravenous morphine equivalents scale. Cerebrospinal fluid was also reviewed when available.
Results There were 53 SAH patients who were treated with GBP along with other analgesics for headache. Among these SAH patients, 34 (64 %) were women, with a mean age of 54 years (SD 12.3). Severe headache was observed in all SAH patients. GBP dosing was rapidly escalated within days of SAH up to a median of 1,200 mg/day, with a range of 300 mg three times a day to 900 mg three times a day. Approximately 6 % of patients treated with GBP had nausea (95 % CI 1–16 %), and only one patient (1.8 %) had to discontinue GBP.
Conclusions GBP appears to be relatively safe and tolerable in SAH patients with headache and may be a useful narcotic-sparing agent to prevent narcotics-associated complications, such as gastrointestinal immobility, ileus, and constipation.

Keywords Aneurysmal subarachnoid hemorrhage · Headache · Meningismus · Gabapentin

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Introduction

Aneurysmal subarachnoid hemorrhage (SAH) accounts for 6–8 % of all strokes and affects up to 30,000 individuals per year in the USA [1]. Headache after aneurysmal SAH is often described as a severe, excruciating pain, or the worst headache of one's life. The classic description of SAH-associated headache is a thunderclap because it begins abruptly and reaches maximal intensity within seconds, consistent with the rapid spread of blood [2]. SAH headache often persists for days to weeks and may require significant amounts of narcotics and other medications

until it subsides. SAH-associated headache may also be neuropathic in origin, given that the meninges are innervated by the anterior and posterior ethmoidal nerves, the tentorial branches of the ophthalmic nerve, and the maxillary division of the trigeminal nerve. Further, over time, the SAH blood is broken down within the subarachnoid space, which may also induce a secondary inflammatory state or aseptic meningitis and meningismus (neck stiffness) [3]. Blood from an SAH also travels to the lower lumbar caudal sac due to gravity, causing delayed lower back pain and even radicular leg pain.

The 2013 European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Hemorrhage recommend acetaminophen and, in cases of severe pain, opiates such as codeine, fentanyl, and tramadol to treat SAH-associated headache [4]. However, opiates are associated with nausea, vomiting, ileus, urinary retention, acute opioid withdrawal, depressed respiratory drive, depressed consciousness, hallucinations, and hypotension [5–12]. Gabapentin (GBP) has been increasingly studied as an opiate alternative for perioperative pain management with the goal of avoiding the documented adverse effects of narcotics. It has been shown to be well tolerated with no major adverse effects. Our center has been using GBP as an agent to reduce opioid requirement for SAH patients. However, there is no published literature regarding the use GBP on this subset of the population.

The primary aim of the study was to evaluate the safety and tolerability of GBP in reducing narcotic use in SAH patients. Our secondary aims were to demonstrate the trend of pain and opioid requirements, along with cerebrospinal fluid (CSF) analysis, and the incidence of seizure, vasospasm, and delayed cerebral ischemia (DCI).

Methods

After Institutional Review Board approval, we conducted a retrospective study of SAH cases treated with GBP who were admitted to the NSICU of Mayo Clinic in Jacksonville, Florida, a tertiary high-volume aneurysm center [13]. The study timeframe was from January 2011 through February of 2013. We reviewed clinical, radiographic, and laboratory data from the electronic medical record using an existing SAH database, as well as by crossmatching against the institutional pharmacy database for GBP use in the NSICU.

The study identified 140 aneurysmal SAH patients during the timeframe. Of this group, we excluded comatose SAH patients who were unable to provide accurate history of pain or pain scale information. Regarding other aspects of the medical management of SAH, including treatment of vasospasm and hydrocephalus, the NSICU team followed the Neurocritical Care Society SAH guidelines [14].

The medical record was reviewed, and data collection included patient demographics, history of tobacco use, hypertension, and Glasgow Coma Scale (GCS) on admission. Recorded laboratory variables included renal function (creatinine and BUN) and liver function tests (aspartate aminotransferase, alanine aminotransferase). Variables regarding surgical treatment included aneurysm clipping or coiling, external ventricular drain (EVD), and lumbar drain placement. Neurological exam and radiological data were reviewed in order to calculate the different score of SAH grading, vasospasm, and DCI. We also reviewed the modified Rankin Scale (mRS) at 30 days and 1-year post-SAH onset.

Pain Assessments

The visual analog scale (VAS) was utilized to quantify pain. VAS has been validated as a reliable indicator to measure pain [15]. The VAS is a standard pain assessment tool in our ICU and was performed per ICU protocol in patients every 4–6 h. We calculated total VAS score each day for headache, excluding other pain like lower back and abdominal pain. If the VAS score is high, the patient is usually administered an opioid and/or occasionally non-steroidal analgesic treatment. We calculated the total daily requirement of the opioid analgesic for each patient. Since there was no uniformity of the drug and doses, we used the opioid dose converter adopted from Shaheen et al. [16] (Table 1) to convert to an intravenous (IV) morphine-equivalent dosage. Other common analgesics were mainly acetaminophen and occasionally ketorolac. Since various studies have compared ketorolac and acetaminophen with strong opioids with conflicting results [17], we did not calculate the dose response in this group (Table 2).

Meningitis Screening

In order to screen for meningitic pain after SAH that was not due to bacterial (septic) meningitis, CSF data from patients who had samples done for standard of care (e.g., for fever or to rule out infection) were analyzed from EVDs, lumbar drains, or lumbar spinal tap fluid. The CSF white blood cell (WBC)/red blood cell (RBC) ratio was

Table 1 Opiate conversion

Products	Equianalgesic oral morphine	Equianalgesic parenteral (IV) morphine (mg)
Morphine	2 mg	1
Fentanyl (IV) 25 mg	–	2.5
Hydromorphone (IV) 1 mg	–	7.5
Oxycodone (PO) 5 mg	7.5–10 mg	2.5

Adapted with permission [16]

Table 2 Patient demographics

Demographic variables	Number (%)
Sex female	34 (64.2 %)
Ethnicity	
Non Hispanic	50 (94.3 %)
Race	
White	36 (68.0 %)
African-American	16 (30.2 %)
	1 Missing
Age (years) mean	54.09 (SD 12.34)
Location	
PCOM	15 (29 %)
ACOM	14 (27.5 %)
Posterior inferior cerebellar artery (PICA)	8 (15.7 %)
Basilar	7 (13.8 %)
Middle cerebellar artery (MCA)	3 (5.9 %)
Other	4 (7.8 %)
	2 Missing
History of hypertension	27 (52 %)
History of tobacco use	26 (50 %)
On statin before admission	15 (29 %)
On beta blocker before admission	8 (15.4 %)
On angiotensin converting enzyme inhibitor (ACEI) before admission	4 (7.7 %)
Coiling	45 (85 %)
Clipping	9 (17 %)
	One had both coiling and clipping
External ventricular drain	29 (54.7 %)
Lumbar drain	3 (5.6 %)
Vasospasm	
Mild-to-moderate	15 (28.3 %)
Severe requiring intervention+	9 (16.9 %)
Death during hospitalization	1 (1.9 %)

plotted each day to gauge the degree of CSF inflammation. The microbiological culture data of the CSF samples were analyzed for any evidence of bacteria or other microorganisms to rule out evidence of bacterial, viral, or fungal meningitis or ventriculitis. When culture was negative and headache persisted, these groups were occasionally treated with a steroid (typically dexamethasone) by the treating neurosurgeon or neuroICU team for presumed "aseptic" or sterile inflammatory. All corticosteroids used were converted into steroid equivalents using a standard conversion table [18].

Vasospasm Detection and Treatment

Since vasospasm (VSP) could conceivably be associated with SAH headache, we graded the presence or absence of VSP based on TCD mean flow velocities (MFV) of the middle cerebral artery in centimeters/second (cm/s). VSP severity was graded as mild-to-moderate for MFVs between 120 and 199 cm/s with Lindegaard ratio $\geq$3.0 and severe VSP being a MCA MFV $\geq$200 cm/s with a Lindegaard ratio of $\geq$6.0 [19]. CT angiography data were also reviewed for the presence or absence of vasospasm as per neuroradiologist-defined vasospasm designated as mild, moderate, or severe. We also reviewed the treatment received for vasospasm, including intrathecal nicardipine, intra-arterial verapamil, or balloon angioplasty. We reviewed the outcome of VSP and subsequent delayed cerebral infarction (DCI) as defined on delayed neuroimaging either on cranial CT or MRI, excluding procedure-related infarctions [20].

Gabapentin Dosing Evaluation and Adverse Effects

The total daily dose of GBP was tabulated for each patient for each hospital day. The medical record was reviewed for any documented adverse effects of the medication by the medical team, a central pharmacy drug adverse event database, as well as documented allergies and nursing notes. Laboratory values were reviewed for any abnormality in hepatic or renal function during the study period.

Statistical Methods

Categorical variables were summarized as percentages, and continuous factors were described using means or medians to best describe the distributions. Adverse events were described as rates, and 95 % confidence intervals were estimated for those rates. The calculated total daily VAS score, opioid score, steroid score, and GBP dose were plotted on a daily basis until day 21 or the discharge date, whichever was earlier. CSF WBC/RBC ratio was calculated from the available samples and trended over time in days after index SAH date. All plotted data were projected with a 95 % confidence interval. JMP version 9.0 (SAS, Inc) was used for statistical analysis.

Results

Over the 29-month study period, we observed 176 total SAH cases, of which $n = 140$ were aneurysmal SAH in nature. Patients with traumatic and perimesencephalic non-aneurysmal SAH were excluded ($n = 36$) from final analysis, as were comatose patients or patients who were unable to provide an accurate history of VAS pain intensity data ($n = 87$). This resulted in the identification of a final 53 consecutive SAH patients who were treated with GBP and other analgesics for headache. Among these SAH patients, 34 (64 %) were women, with a mean age of

54 years (SD 12.3). Posterior communicating (PCOM) was the most common type of aneurysm (15; 29 %) followed by anterior communicating (ACOM) (14; 27 %). Approximately half of the patients had prior history of hypertension and tobacco use. Coiling was the preferred method of intervention (45; 85 %), and more than half of those patients had EVD placement. More than 82 % of the SAH patients presented with a GCS score of >9 on admission. Sixty-eight percent had a modified Fisher score of ≥ 3 at admission. Table 3 summaries the distribution of patients according to different SAH scores. There were 31 (70 %) patients who had a 30-day modified Rankin score (mRS) of <3. Nine patients were lost to follow-up for mRS assessment by 30 days. We presume some of this might be due to being followed up by local doctors who were not within our health network.

Among the 53 study patients, 24 % were started on GBP within the first day of admission, which increased to 88 % by day 5 after SAH. The average starting dose for GBP was 100 mg three times a day, and by day 7 after SAH, the range of GBP daily dose was from 300 to 2,700 mg (900 mg three times a day). The escalation of GBP for most patients was individualized and based on their headache response and narcotic use. Every day during morning rounds, SAH patients were assessed regarding their headache control with opioid or steroid, and if they still were experiencing severe headache, the dose of GBP was increased. The typical escalation was 100 mg three times a day to 300 mg three times a day and then 600 mg three times a day followed by 900 mg three times a day. There was one patient who was already on 100 mg of GBP three times a day at home for neuropathy, which was escalated to 300 mg three times a day to control the headache.

With regard to reported adverse effects, only three patients (6 %) had nausea documented while on GBP (95 % confidence interval of 1–16 %), of which only one patient (1.8 %) abruptly discontinued GBP due to nausea. There were no serious adverse events or other safety events in these patients. Among these three patients with nausea, Patient #1 tolerated the rapid titration of GBP to 600 mg three times a day on day 7 and stayed on this dose until day 22. We believe that in this case, nausea may have been concomitant with headache or other factors. Patient #2 did not tolerate GBP and was discontinued on day 9 after a dose of 300 mg three times a day was tried for 3 days. Patient #3 experienced nausea but tolerated 200 mg of GBP three times a day until day 19 and was discharged without it. One patient receiving enteral GBP via an NG tube later died during hospitalization but was unrelated to GBP. This patient had medically refractory high intracranial pressure and herniation due to global cerebral edema.

We searched for any unexplained depression, peripheral edema, ataxia, dizziness, nystagmus, and somnolence as outlined in the package insert for other adverse effects with the drug GBP. None of these adverse effects were documented during the study. Laboratory data on liver function tests were reviewed, and no significant rise in transaminase

Table 3 Admission SAH score and mRS at 30 days and 1 year

Hunt and Hess at admission	
0	1 (2.1 %)
1	14 (29.2 %)
2	10 (20.8 %)
3	15 (31.3 %)
4	4 (8.3 %)
5	4 (8.3 %)
Missing = 5	
World Federation of Neurologic Surgeons (WFNS) at admission	
0	1 (2.0 %)
1	25 (49.0 %)
2	7 (13.7 %)
3	4 (7.8 %)
4	9 (17.7 %)
5	5 (9.8 %)
Missing = 2	
Glasgow Coma Scale (GCS) at admission	
≤8	9 (17.65 %)
9–13	9 (17.65 %)
>14	33 (64.70 %)
Missing = 2	
Modified fisher	
1	5 (10 %)
2	11 (22 %)
3	11 (22 %)
4	23 (46 %)
Missing = 3	
Modified Rankin Scale (mRS) 30 days	
0	18
1	7
2	6
4	2
5	1
6	
Missing = 9	
mRS at 1 year	
0	16
1	4
2	0
3	1
4	1
5	0
6	2
Missing = 29	

levels was noted during GBP use. There were no patients with renal failure who required renal-dose titration in this study. GBP when tabulated against the days of hospital stay (Fig. 1) showed a sharp rise in the total daily dose until day 4 and then slowly plateaued until day 21. In most of the patients, GBP dose was rapidly decreased and stopped typically within days to weeks after discharge.

Secondary Aims Data

VAS and Opioid Requirement

While calculating the total daily VAS, we only included head pain (proper) for the total daily pain score calculation and took the average among all of the patients. We observed that the average pain score on day 1 of hospital admission was 11, which rose to maximum of 26 by day 4. Interestingly, there were (Fig. 2a) two different, subsequent headache pain peaks numerically noticed on day 11 and day 16. The daily opioid requirement in morphine equivalents only for headache pain showed a sharp rise from day 1 until day 6, a gradual decrease over next 16 days followed by a secondary peak in pain around days 15 and day 19. Overall, there was a gradual decreasing trend along with opioid score (Fig. 2b).

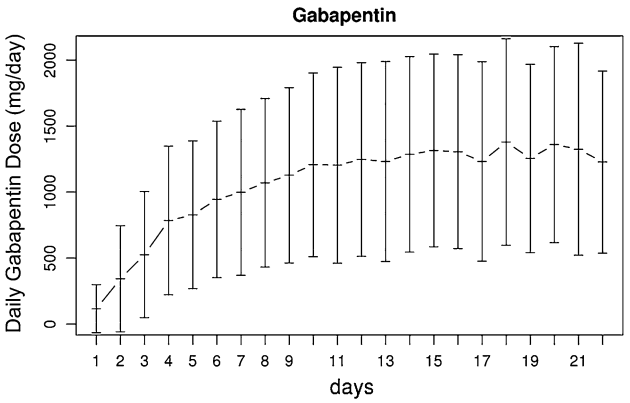

Fig. 1 Total daily gabapentin dose and confidence interval

Vasospasm and Delayed Cerebral Ischemia Data

VSP was noted in a total of 24 (45 %) patients. Severe and symptomatic vasospasm was noted by transcranial Doppler and/or CT angiography in 9 (17 %) patients and was treated with a combination of medical augmentation or intrathecal nicardipine, intraarterial verapamil, or balloon angioplasty at the discretion of the treating neurointensivists or neurosurgeon. DCI was ascertained by review of CT/MRI by the 6-week post-SAH mark. New DCI-defined infarction was noted in 23 (43 %) of SAH patients. Five patients (6 %) developed a radiological infarct in the same vascular territory of the VSP

Cerebrospinal Fluid Analysis and Steroid Use

None of the SAH patients developed bacterial meningitis. However, CSF WBC/RBC inflammatory ratio tended to peak around day 13 post-SAH and again on day 18 (Fig. 3). This interestingly correlated with the delayed headache on VAS noted above. The use of steroid increase during the latter half (Fig. 4). One of the CSF samples grew *E. fecalis,* but this was retested and was deemed to be a contaminant by Infectious disease consultant

Seizures and Antiepileptic Drugs

Levetiracetam was used prophylactically in 27 patients. Four patients had EEG-documented seizure and received antiepileptic drug (AED) medication. All patients with either clinical or electrographic seizures were placed on maintenance levetiracetam 500 mg twice a day for seizure prophylaxis. Two patients had a prior seizure history but

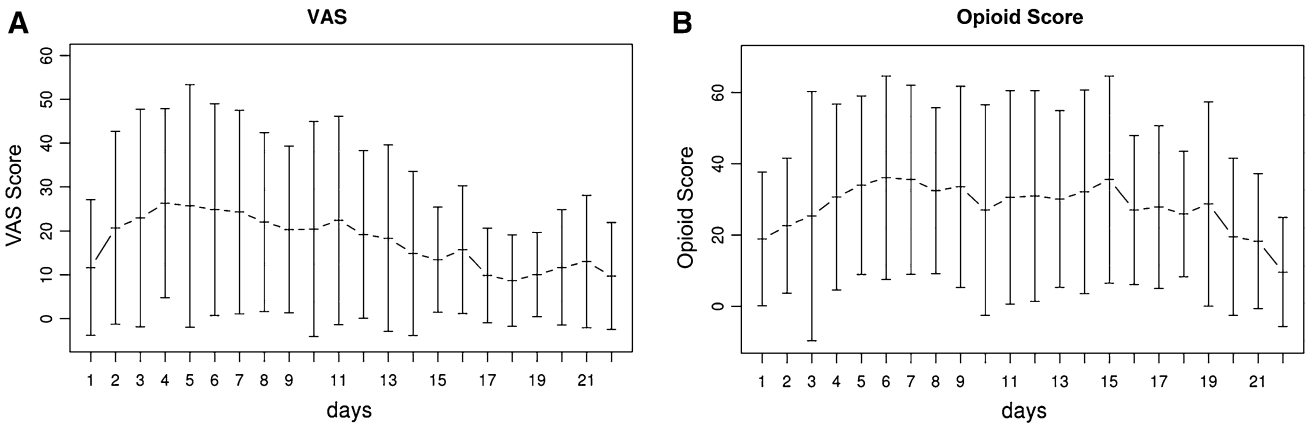

Fig. 2 Total daily VAS (**a**) and opioid score (**b**) and confidence interval

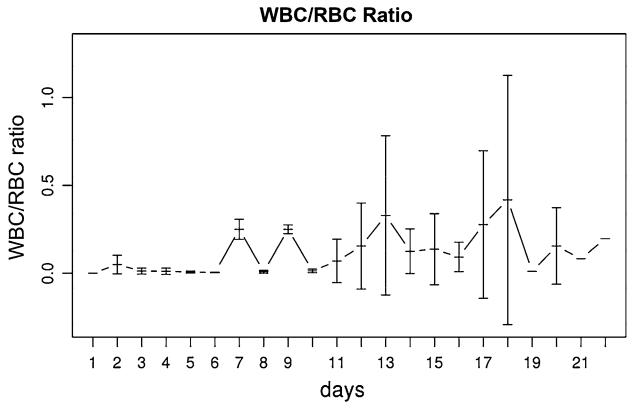

Fig. 3 Cerebral spinal fluid (CSF) white blood cell/red blood cell (WBC/RBC) ratio and confidence intervals

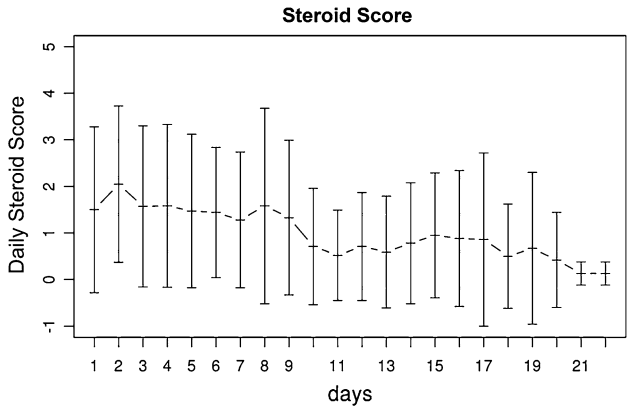

Fig. 4 Total daily steroid score and confidence intervals

did not experience seizures during their SAH admission. One patient was on levetiracetam, and the other was on phenytoin at home.

Study Limitation

This was a single-center, retrospective, observational study with a limited number of patients, which prevented us from having any conclusive evidence on the efficacy of GBP in this patient population. The results could have been confounded due to the non-randomized administration of GBP, variable dosing, use of nonsteroidal anti-inflammatory drugs or steroids, and other differences among the patients.

Discussion

Gabapentin has been increasingly studied as an opiate alternative for perioperative pain management with the goal of reducing the use of narcotics. GBP is a structural analog of γ-aminobutyric acid (GABA) [21]. Despite GBP having structural homology to GABA, there is no conclusive evidence yet that GBP blocks GABA. GBP reduces neuropathic pain by decreasing the release of glutamate, norepinephrine, and substance P [22]. The history of the clinical use of GBP began in 1993 after FDA-approval for the treatment of partial seizures and secondary approval for postherpetic neuralgia in 2002. Currently, it is used as an effective analgesic in different types of neuropathic pain syndromes [23]. It has been tolerated well without any major adverse effects. Since GBP has previously been a common therapy for headache patients, its use has been extended to SAH patients in our institute.

There is no published literature on the use of GBP among SAH patients. This is the first retrospective study looking at the safety and tolerability of oral GBP. The rational of using GBP for other types of headache was that, as an alpha-2-delta receptor (A2DR) analog, it decreases calcium influx decreasing the neurotransmitter release [24]. A study regarding GBP use on neuropathic pain in the ICU was conducted among 18 Guillain-Barré Syndrome (GBS) patients and showed decreased numeric pain score, decreased need of fentanyl, minimal sedation, and safety of rapid titration of GBP [25]. Not only can GBP decrease pain, but due to its unique effects in neuronal receptors, it has been shown to reduce seizure, reduce stroke infarct size, and decrease the cortical spreading depression (CSD) which are implicated in vasospasm and DCI [22].

Narcotics are commonly used in SAH patients yet have significant adverse effects including narcotic-related ileus, constipation (20–60 %), pruritus (0–30 %), urinary retention (40–45 %), hypoventilation, acute withdrawal syndromes during drug weaning, and delirium [5–9]. Many studies have also shown that high doses of narcotics can cause delirium and can prolong ICU length of stay (LOS) by as much as 8–24 days [8, 10]. On average, a 5-day stay in the ICU is estimated to cost US hospitals US$17,000 for such neurocritical patients [11]. ICU LOSs are also among the top three areas of highest cost in treating patients with acute SAH [12].

We focused our study on the safety and tolerability of GBP in order to determine the feasibility for a future case–control study or prospective, randomized trial. In our study, we did not find any serious or life-threatening adverse events with GBP therapy. Those patients who experienced nausea were also on concomitant narcotics which are associated with nausea. In this study, nausea was symptomatically managed with standard anti-emetic treatments such as IV ondansetron, prochlorperazine, or promethazine. Nausea may also be part of severe headache syndromes, and it is difficult to isolate GBP as the sole contributing factor. We did have one patient who stopped the drug empirically due to nausea, but there was no other clinical or laboratory evidence of GBP-adverse effects in that patient to suggest hepatitis or pancreatitis.

Further, some interesting observations were made during this study. When we reviewed the trend on the VAS, opioid use, and GBP dosage pattern, we saw a gradual decreasing trend in the VAS and opioids used as the GBP dosage peaked, but since this was just an observational study without a control group, we are not able to make definite conclusions about dose–response relationships. Nonetheless, the findings suggest decreasing trend of opiate use and pain scale score with GBP use. In addition, recent Clinical Practice Guidelines for the Management of Pain in the ICU recommended that enterally administered GBP in addition to IV opioids could be considered for the treatment of neuropathic pain (+1A) [6]. Since there is a significant number of patients who go through craniotomy and clipping of their aneurysm, GBP might be useful during the perioperative period because it has been studied extensively in anesthesia and perioperative period and has been shown to reduce analgesic, particularly opiate, consumption, and associated adverse effects. Postoperative craniotomy pain is also known to affect superficial cranial nerves, which may be neuropathic pain generators. However, not all SAH patients were treated with clipping and central neuropathic pain generators from meningeal-trigeminal innervated nerves suspected to be the cause for SAH-related headache. SAH patients on GBP may also benefit from GBP's co-existent anxiolytic, antiemetic, antiepileptic, antipruritic, and postoperative pain-reducing effects [6, 24–26].

Gabapentin's antiepileptic effects in SAH patients are also a potentially beneficial side effect, particularly for SAH seizure-prone patients or those with SAH seizures at onset who later awaken with headache. Studies have shown that the incidence of seizures following aneurysmal SAH is 4–22 % [27, 28]. In this study, we had a 7.5 % incidence of seizures, although the doses used in this study were primarily for pain control. GBP is not FDA-approved for primary seizure control but is approved as an adjunctive anti-epileptic drug. All of the patients in this study who experienced seizure were on AED prophylaxis with levetiracetam due to its low sedating potential and minimal drug–drug interaction. We unfortunately cannot estimate whether there was any reduction in seizure activity occurred with the use of GBP among our study patients because this would have required a different study design. Theoretically, GBP should have synergistic AED action with levetiracetam and potentially reduce the incidence of seizures. We also noted that no patient had a seizure with weaning or discontinuation of GBP in this study at the doses used.

Finally, a secondary observation worthy of mention is the two "inflammatory peaks" in CSF WBC/RBC data, which also coincided with breakthrough pain for which steroids seemed to be used due to refractory SAH pain for which GBP and narcotics and other agents may not have worked as well. This is an important observation into the pathogenesis of SAH-related headache and pain. These data suggest that SAH may trigger an initial severe headache from blood on the meninges that is neuropathic or related to intracranial pressure and that a second type of pain occurs that is delayed and due to sterile CSF inflammation caused by the breakdown products of blood. SAH blood products that breakdown over 1–2 weeks after aneurysm rupture with oxyhemoglobin blood products are known to cause intense inflammation, which can cause vasospasm and even DCI and other inflammatory complications. While GBP does have an A2DR receptor function, it may not have enough anti-inflammatory effect to reduce vasospasm and DCI. Nonetheless, GBP's co-existent drug properties make it worthy of future study, given its pleiotropic effects on narcotic-reducing pain effects, A2D receptor effects, and potential antiepileptic drug effects given the risks of seizure in this population. Therefore, despite the retrospective nature of this study with its inherent limitations, we hope this study will serve as a benchmark and feasibility study for future prospective trials. We concluded that GBP 100–900 mg taken three times a day by mouth in this subgroup of patients is reasonably safe and tolerable.

Conclusion

GBP appears relatively safe and tolerable in aneurysmal SAH patients. Secondly, SAH headache pain may occur in 2–3 "waves" consisting of an initial neuropathic pain after SAH within the first week, followed by delayed second and third waves of possible CSF inflammatory pain around 7–10 and 14 days. A larger prospective, randomized study is planned to study GBP in acute SAH patients.

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Conflict of interest The authors report no conflicts of interest or financial relationships relevant to this work and no ties to the pharmaceutical industry.

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