RESEARCH ARTICLE OPEN ACCESS

Pain Management in Aneurysmatic Subarachnoid Haemorrhage: A Survey of Nordic Physicians

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Received: 8 August 2025 | **Revised:** 9 January 2026 | **Accepted:** 14 January 2026

ABSTRACT

Background: Headache caused by aneurysmatic subarachnoid hemorrhage (aSAH) is often severe and may persist long after the ictus. Pharmacological pain management can be challenging due to poor efficacy or adverse effects. Multimodal pharmacotherapy is often required. Lack of guidelines and good quality clinical studies on pain management has led to variation in pain management practices. Knowledge of current practice and goals of pain management in Nordic countries is lacking. We aimed to fill these knowledge gaps by conducting a survey targeting Nordic clinicians involved in aSAH treatment.

Methods: An electronic survey in English was sent to national coordinators in December 2023. The coordinators distributed the survey to intensivists, neurosurgeons, and other specialists treating aSAH patients in their respective countries. The survey contained 63 questions gathering background information, current aSAH pain management during the hospital stay and at hospital discharge, follow-up, and preferred outcome measures regarding a clinical trial on pain management in aSAH. The results were analysed and presented descriptively.

Results: We received 70 responses: 36 from Finland, 11 from Norway, 11 from Denmark, 5 from Sweden and 7 from Iceland. Respondents were intensivists ($N=46$), neurosurgeons ($N=20$), neurologists ($N=2$), and others ($N=2$). The most frequently used pain medications at ICUs were paracetamol, opioids, and non-steroidal anti-inflammatory drugs (NSAID). Most neurosurgeons (70%, $N=14$) responded that they never prescribe opioids at hospital discharge for aSAH patients. The most preferred outcome for a clinical trial was patients' self-reported quality of life.

Conclusions: In the Nordic countries, paracetamol, opioids, and NSAIDs were reported as the most frequently used analgesics in the management of aSAH related pain in the ICU. Use of gabapentinoids was commonly reported by Danish respondents, unlike respondents from other Nordic countries. Neurosurgeons reported that they rarely prescribe opioids at hospital discharge.

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Editorial Comment: This survey of Nordic clinicians involved in ICU and neurosurgical management of subarachnoid bleed (aneurysm) cases presents preferences for pain management in hospital and with discharge, as well as assessing clinician preferences for outcomes by which to assess pain management in these cases.

1 | Introduction

Subarachnoid hemorrhage (SAH) is a life-threatening medical condition. Most of the spontaneous SAHs (85%) are caused by rupture of an intracranial aneurysm (aSAH), 10% are non-aneurysmatic, and the rest are caused by rare medical conditions such as arteriovenous malformations [1]. In aSAH the ictus is commonly characterized by a sudden severe headache ("thunderclap headache") which can be difficult to manage and may persist even years [2–4]. More than half of conscious patients with aSAH report severe pain that persists during the acute phase and hospitalization despite routine use of pharmacological analgesics [5, 6]. Pain associated with aSAH is considered to be multifactorial involving inflammatory mechanisms and meningeal irritation caused by the blood in the subarachnoidal space. Dysfunction in autoregulatory mechanisms in cerebral perfusion and vasospasm may increase the headache [7, 8]. In addition, endovascular or neurosurgical treatments may cause pain, and chosen treatment may affect the short- and long-term pain relief [9, 10].

For decades, pain management of aSAH patients has relied heavily on paracetamol and opioids even though they lack efficacy, and especially opioids are associated with adverse effects. To improve pain management, different adjuvants, such as gabapentinoids, non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics, magnesium, and corticosteroids have been used, despite lack of evidence from high quality clinical studies [11]. In a recent international survey, the most frequently used adjuvants were antiseizure medications and corticosteroids, but most of the responses originated from North America, and the preferred adjuvants may differ in the Nordic countries [12]. An updated guideline by the American Heart Association/American Stoke Association (AHA/ASA) also highlights the gap in knowledge when it comes to management of aSAH associated pain [13].

There is currently no clear consensus on the most appropriate outcome measures for patients with aSAH. However, recent surveys have laid the ground for developing a core outcome set (COS) for aSAH patients. These studies have highlighted that healthcare providers and patients may have different views on which outcomes are most important. To support the patients' recovery, the identification of shared outcomes that reflect both clinical relevance and patient-centered goals is crucial [14, 15].

The aim in this study was to investigate the management of aSAH-related pain in the Nordic countries, with particular focus on the use of gabapentinoids as adjuvant analgesics. In addition, we wanted to identify the outcome measures considered most relevant for a future randomized controlled trial on pain management in patients with aSAH.

2 | Methods

2.1 | Study Design, Data Collection and Approvals

We conducted a cross-sectional international study across all five Nordic countries using an electronic survey administered in English. The questionnaire was formed based on knowledge gaps in aSAH pain management since no validated questionnaires on this subject existed. The questionnaire was pre-tested, adjusted, and approved by the research group, as well as by three anesthesiologists specialized in neuroanesthesia and a neurosurgeon working at the Tampere University Hospital. Pretesters reflected the sample population.

Responding to the survey was voluntary and anonymous, and no financial compensation was provided to the respondents. The first item was an informed consent, and the rest of the questionnaire opened only after the consent was given. Approval of the study was obtained from the Wellbeing Services County of Pirkanmaa (R24281, 3.10.2023). The survey did not include patient data and thus the approval from an ethics committee was not needed.

2.2 | Survey Description

The survey contained 63 questions. We gathered background information concerning the hospital and clinic. No identifying personal data were collected. Respondents were asked about the management and monitoring of pain in non-traumatic SAH patients throughout the entire hospital stay (ICU, ward and hospital discharge). The questions included selecting a preferable order between different medications and in some questions choosing the three most preferred medications (no specific order). Even if the respondent did not specifically participate in some parts of the patients' treatment, they were allowed to give their opinion. Questions about follow-up arrangements and the preferred outcome measures were at the end of the questionnaire. The questionnaire is presented in Table S1.

2.3 | Survey Distribution

We identified local coordinators from all Nordic countries (Five from Finland, four from Denmark, one from Iceland, one from Norway, one from Sweden) who distributed the survey in their own national networks. In Finland, the survey was distributed to five, in Sweden seven, in Denmark three, in Norway four, and in Iceland one unit treating aSAH patients. The survey was sent to specialist professionals participating in the treatment of aSAH patients in ICUs and/or at hospital wards. We sent two reminder messages (21.12.2013 and 5.1.2024) to maximize the response rate. We distributed the survey and collected the responses between December 1st, 2023, and January 31st, 2024.

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Details about the distribution are presented in Table S2. There was no specific method to prevent multiple participation.

2.4 | Statistics

We analyzed the data with IBM SPSS Statistics 29.0 (IBM, Armonk, NY, USA) and Excel version 2508 (Microsoft, Redmond, Washington, USA) and present the results both graphically and descriptively. We report the studied variables as the number of specific responses and their percentage from all the responses obtained. To form preferred order in pain medication, we calculated how many times each medication was ranked 1st, 2nd, 3rd, etc. The number of votes for each ranking was divided by the number of respondents to that question resulting in proportions for each ranking. These proportions were then converted into weighted points by multiplying 1st ranking by 10, second by 9, third by 8, etc. Finally, the sum of all weighted points, separately for each medication, was calculated. In this article, these results are referred to as weighted ratio. We used the same method for analyzing the preferred outcome measures. We dismissed responses “other” without additional information.

We report the results according to CROSS guideline for reporting survey studies [16].

3 | Results

3.1 | Demographics

Of the 328 professionals who received the survey, 70 (21%) responded, covering all five Nordic countries. The demographics of the respondents are shown in Table 1. All respondents were physicians treating aSAH patients in a university hospital.

Most of the respondents (81%, $N = 57$) reported that they participated in pain management primarily in the ICU. Half of the respondents (54%, $N = 38$) reported that more than one specialty is responsible for the management of aSAH patients in the ICU, whereas 30% ($N = 21$) reported that intensivists alone are responsible for these patients in the ICU. Four out of five Norwegian neurosurgeons reported that neurosurgeons have the primary responsibility alone for the aSAH patients in their ICU. They also reported that they participate in pain management primarily in the ICU. All respondents answered the question about preferred pain medication in the ICU, although four (6%) stated that they do not participate in pain management in the ICU.

According to 74% of the respondents, pain is systematically monitored in their ICUs, mostly with Visual Analog Scale (VAS) (59%, $N = 41$), Numeric Rating Scale (NRS) (53%, $N = 37$), and Critical Care Pain Observation Tool (CPOT) (30%, $N = 21$). Also, 74% reported that standardized operating procedure for pain management exists in their ICU.

According to 41% ($N = 29$) of respondents, patients are invited to a follow-up visit, usually meeting with a neurosurgeon approximately 3 months after hospital discharge.

TABLE 1 | Characteristics of the respondents.

	***N* (% response rate per country)**
Finland	36 (21)
Anesthesiology and intensive care	20
Neurosurgeon	12
Neurology	2
Other	2
Sweden	5 (36)
Anesthesiology and intensive care	3
Neurosurgeon	2
Norway	11 (42)
Anesthesiology and intensive care	6
Neurosurgeon	5
Denmark	11 (12)
Anesthesiology and intensive care	10
Neurosurgeon	1
Iceland	7 (30)
Anesthesiology and intensive care	7

3.2 | Preferred Pain Medication

The top five most preferred pain medications during the ICU admission are shown in Figure 1. The top three pain medications were paracetamol, opioids, and NSAIDs, respectively. Ten respondents reported corticosteroids as other alternatives, ranking them in the top five. Seven responded that they use clonidine for aSAH-related pain. Dexmedetomidine and Fenazon-Koffein (combination of phenazone and caffeine) were also used. The top five pain medications used in the ICU were selected by 70, 70, 70, 69, and 68 respondents, respectively. The reduction is due to added information where respondents said they use only three or four medications from the list.

3.3 | Opioids

In the ICU, preferred opioids were intravenous (i. v.) oxycodone and fentanyl. At hospital discharge, six (30%) neurosurgeons reported occasional prescription of opioids, mainly weak opioids (tramadol or codeine) or orally administered extended-release oxycodone combined with naloxone. Most neurosurgeons (70%) responded that they never prescribe opioids at hospital discharge for aSAH patients.

3.4 | Non-Steroidal Anti-Inflammatory Drugs

The top three preferred NSAIDs were coxibs, ibuprofen, and naproxen. Some respondents mentioned specifically that NSAIDs were only used after the aneurysm is secured, and 27

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(39%) respondents, including all Danish respondents, answered that NSAIDs are not used in the ICU for aSAH patients.

3.5 | Gabapentinoids

Gabapentinoids were generally not used but there were major differences between respondents from different countries. Use of gabapentinoids was most frequently reported by Danish respondents, in the ICU almost half of the respondents ($N=5$) chose gabapentinoids as third option. However, half of all respondents ($N=35$) answered that gabapentinoids are not used for pain management indication in aSAH patients in the ICU. In hospitals where gabapentinoids were used, gabapentin was preferred over pregabalin.

3.6 | Preferred Outcomes and Outcome Measures

According to the respondents' opinion, the three most important outcomes assessing recovery after aSAH were (health related) quality of life (measured by any standardized form), cognitive functioning, and survival (Figure 2). In free text answers, respondents brought up the importance of assessing the wellbeing of relatives when meeting at the follow-up.

The respondents also rated different aSAH outcomes on a scale from one to five considering the importance of an issue. Many of the aspects received a high score, but the highest score in this listing was received by "managing activities of daily living independently" followed by "preserved cognitive functioning". This different way to ask about the outcomes revealed that all the outcomes were considered at least moderately important. More details are shown in Figure S1.

4 | Discussion

With this cross-sectional international survey to Nordic physicians participating in the management of aSAH patients, we captured an overall image of acute pain management of aSAH patients in the ICU and which outcome measures are valued by physicians who participate in the treatment of aSAH patients. According to our results, paracetamol, opioids, and NSAIDs are the most frequently used medications for aSAH analgesia in the ICU. Corticosteroids are most often considered as co-analgesics. Gabapentinoids were commonly used in Denmark in the ICU, but in other countries, they were not in regular use despite recent studies suggesting that they may reduce opioid consumption and have neuroprotective qualities [17, 18]. Other valuable effects of gabapentinoids are their anxiolytic effect and probable positive effect on insomnia [19]. The cautious attitude toward gabapentinoids may originate from reported adverse effects such as sedation and dizziness, predisposing the patients to falls, weight gain, synergistic

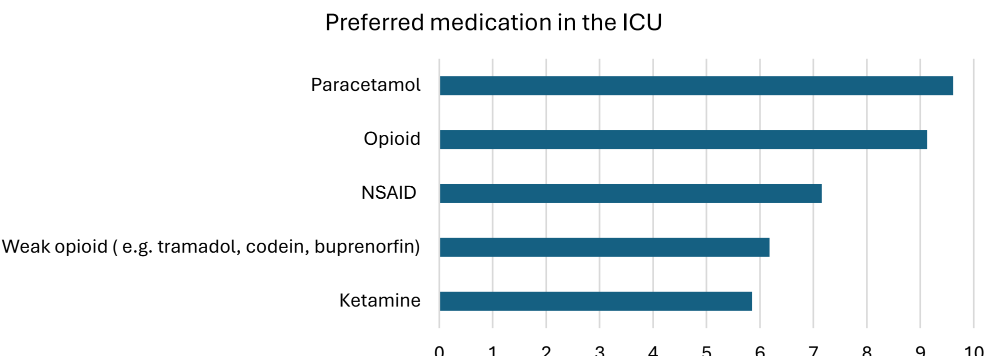

FIGURE 1 | Preferred pain medication in the ICU. Weighted ratio. For details, please refer to Methods.

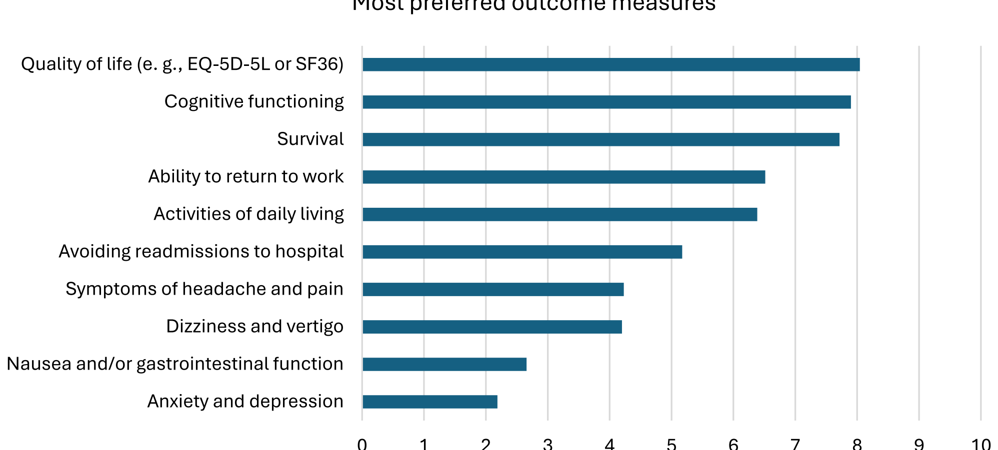

FIGURE 2 | Most preferred outcome measures, listed in preferred order. Weighted ratio. For details, please refer to Methods.

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respiratory depression with opioids, potential for substance abuse and blurred vision [20, 21].

The major difference between our survey and a recent worldwide survey is the frequent use of NSAIDs in most Nordic Countries [12]. Probably the fear of rebleeding has been the major reason why the use of NSAIDs has been scarce elsewhere even though recent evidence suggests that after securing the aneurysm they are safe and may have even some neuroprotective qualities [22].

Opioids are frequently used in the ICU, but unlike in North America or other parts of Europe, it seems that in Nordic countries prescribing opioids at hospital discharge after aSAH is rare. In general, the difference in opioid use between the United States and Europe is likely multifactorial, extending to opioid prescription after aSAH [12]. In aSAH, there may also be differences with discharge locations. In this survey, we asked if the respondent prescribes opioids at hospital discharge, but prescribing medications is not applicable if the patient is transferred to step-down hospitals after acute treatment of aSAH, which may confound the results.

In our survey, physicians responded that managing everyday life independently is the most appreciated outcome in aSAH related research. Other highly valued outcome measures evaluated by the respondents for aSAH patients were quality of life (reported by the patient), cognitive functioning, and survival. Our results align with two international surveys by Anderson et al. that aimed at developing a core outcome set for future aSAH research. They found that the most appreciated outcome measures were patient-reported quality of life and cognitive functioning. According to our survey, physicians in Nordic countries appreciate the same outcome measures as most stakeholders worldwide, but unfortunately, they are seldom reported [14, 15].

Pain management is rarely highlighted in aSAH management protocols despite the frequent use of clinical scoring like the Hunt and Hess grading scale, which depends heavily on headache as a symptom [13, 23]. Also in this survey, many of the respondents did not list pain as a highly relevant symptom of aSAH patients. In our view, this may reflect the severity of this disease, where patients often have several other major symptoms, such as impairment in cognitive function or physical disabilities. However, in aSAH patients, persistent headache is associated with increased weariness, sleep disturbances, and cognitive dysfunction which may impair their quality of life [24].

4.1 | Strengths and Limitations

With this survey, we received valuable information about commonly used pain medications in aSAH in Nordic countries. To our knowledge, our study is the first one assessing the pain management of aSAH in the Nordic countries. However, our study has limitations. The response rate was very low (21%), and those who responded to the questionnaire may have been more enthusiastic about the topic, and response bias cannot be excluded. Response rates in other surveys in the field are often either unreported or similarly low [12, 25].

The questionnaire also included questions concerning pain management at the hospital ward after discharge from ICU. However, though most of the respondents gave their opinion about the pain management at the ward, their role in pain management at that phase remained unclear due to limitations in the structure of our questionnaire. Thus, we were unfortunately not able to report reliable results throughout the hospital stay.

The survey recipients accurately represented the intended study population, specialists working in university hospital ICUs. According to the guidelines, in the acute phase, aSAH patients should be treated only in university hospital ICUs and by a specialized group of physicians [13]. As most respondents were from Finland, Finnish practices may have had a larger impact on the results. Nevertheless, since the coordinators distributed our survey to 20 out of 21 units treating aSAH patients in the Nordic countries, we trust that the responses are representative for all Nordic countries, including current medical practice in pain management and physicians' preferences. However, a clustering effect inherently remains, due to an uneven number of responses from each institute.

In this survey the respondents evaluated pain management for patients with spontaneous SAH; since most cases are due to aneurysm rupture, we consider that the results reflect the pain management in aSAH, especially since spontaneous non-aneurysmatic SAH is reported to cause less pain than aSAH [26].

In our questionnaire, corticosteroids were not given as alternatives, which may cause underestimation of corticosteroid use. Several respondents reported corticosteroid use in the open responses.

Finally, some respondents suggested in free text that the wellbeing of relatives is an important outcome. This question or topic was not included in the questionnaire but might have been assigned priority by the respondents if included.

4.2 | Conclusion

In the five Nordic countries, paracetamol, opioids, and NSAIDs are perceived as the three most important/frequently used pharmacological agents for treating pain in aSAH patients. Use of gabapentinoids was commonly reported by Danish respondents, unlike respondents from other Nordic countries. Opioids are rarely prescribed at hospital discharge, although they are commonly used during hospital stay.

Author Contributions

Hanna Sariola: conceptualization, data curation, investigation, formal analysis, methodology, visualization, writing (original draft). **Johanna Hästbacka**, **Maija-Liisa Kalliomäki:** conceptualization, methodology, supervision, validation, writing (review and editing). **Heikki Kiiski**, **Essi Raatikainen**, **Juhana Frösen:** questionnaire pre-testing, data collection, writing (review and editing). **Matti Reinikainen**, **Terhi Lohela**, **Kirsten Møller**, **Riikka Takala**, **Martin Sigurdsson**, **Luis Romundstad**, **Stig Dyrskog**, **Karsten Bülow:** data collection, writing (review and editing). **Hanna Savioja:** writing (review and editing).

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Acknowledgments

We thank Elina Manelius for expert help. We thank Kati Järvelä and Pia Puolakka for their comments on the manuscript. Open access publishing facilitated by Tampereen yliopisto ja Tampereen ammattikorkeakoulu, as part of the Wiley - FinELib agreement.

Funding

This work was supported by Suomen Anestesiologiyhdistys; State funding for university-level health research, Tampere University Hospital, Wellbeing services county of Pirkanmaa, Project number T63804.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Survey questionnaire. **Table S2:** Survey distribution. **Figure S1:** The importance of issues considering outcome after aSAH ranked from one "not important" to five "very important".

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