Unaccounted for enteral volume loss linked to delayed cerebral ischemia after subarachnoid hemorrhage

Chloé Louise Gelder, MBBS,¹ Melissa Bautista, MBChB,¹ Sidra Arif Awan, MPharm,² and Ian A. Anderson, FRCS(SN)¹

¹Leeds General Infirmary, Leeds; and ²University College London Hospital, London, United Kingdom

OBJECTIVE Delayed ischemic neurological deficit (DIND) is seen as a clinical manifestation of cerebral vasospasm and is a significant cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage (aSAH). Currently, the standard of care for DIND prevention in patients who have sustained aSAH is prophylactic nimodipine therapy and ensuring adequate fluid intake, alongside other treatments such as bowel care. Osmotic laxatives trap water within the bowel lumen to accelerate the transport of the gut contents through the bowel. Given the potential for DIND secondary to cerebral vasospasm, it is perhaps counterintuitive that gastrointestinal fluid loss and use of osmotic laxatives are not commonly considered in many aSAH management protocols.

METHODS A retrospective case note analysis was performed for all adult patients (aged > 16 years) admitted to the Department of Neurosurgery at Leeds General Infirmary with a diagnosis of aSAH between August 2019 and September 2020.

RESULTS A total of 105 patients were included, 62% of whom were female, with a mean and median age of 54 years (range 24–84 years). Diarrhea was noted in 12 patients (11.4%), 58% of whom subsequently developed DIND (OR 15.30, CI 3.92–59.14; $p = 0.0001$). All patients received osmotic laxatives (97% having received ≥ 2 laxative agents).

CONCLUSIONS Patients with aSAH who subsequently developed diarrhea had significantly increased odds of developing DIND. Enteral volume loss due to osmotic laxative use is a potential risk factor for DIND after aSAH.

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KEYWORDS laxatives; subarachnoid hemorrhage; cranial vasospasm; intracranial vasospasm; intracranial aneurysm

CEREBRAL vasospasm refers to the phenomenon of cerebral arterial vasoconstriction that commonly occurs 7 to 10 days after ictus of aneurysmal subarachnoid hemorrhage (aSAH). Delayed ischemic neurological deficit (DIND) is defined as “a delayed neurological deterioration with fluctuations in consciousness and/or development of focal neurological symptoms not attributed to any other cause.”¹ DIND is seen as a clinical consequence of cerebral vasospasm and is a significant cause of morbidity and mortality following aSAH.²

Currently, the standard of care for DIND prevention in patients who have sustained aSAH is prophylactic nimodipine therapy³ and ensuring adequate fluid intake, typically, at least 3 L of fluid per day. Alongside these treatments, other symptomatic medical management may be started

for patients with aSAH, including analgesia and bowel care. Aperients are often part of the aSAH management protocol on admission; until the aneurysm is treated, it is thought that excessive straining should be avoided (due to concerns about the potential effects of any Valsalva maneuver on intracranial pressure). Furthermore, constipation is often encountered in patients with restricted mobility and those receiving opiate analgesia.^{4,5}

The human body keeps a tight regulation on its fluid balance. Blood plasma contains approximately 7% of the body's total fluid content; there is around 3 L of fluid in the blood plasma. The large intestine allows significant active absorption of as much as 5 to 8 L of fluid and electrolytes per day. Overall, only approximately 100 ml of water is lost in the feces per day. Even with fluid maintenance or

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; DIND = delayed ischemic neurological deficit; LOS = length of stay.

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increased fluid intake, given that the large intestine can absorb 5 to 8 L of fluid per day, a patient can still be in a negative fluid balance if they have increased enteral loss.⁶

Osmotic laxatives trap water within the bowel lumen to accelerate the transport of the gut contents through the bowel.⁵ Commonly used osmotic laxatives include lactulose and other macrogol treatments, and they can have adverse effects such as diarrhea, dehydration, and electrolyte disturbance.⁷

With impaired autoregulation, inadequate intravascular volume, and vasospasm, patients often become symptomatic.⁸ Given the potential for DIND secondary to cerebral vasospasm, it is perhaps somewhat surprising that gastrointestinal fluid loss and use of osmotic laxatives are not commonly considered in aSAH management protocols. The European Stroke Organization guidelines for management of intracranial aneurysms and SAH states that “to avoid situations of increased intracranial pressure... the application of... laxatives should be considered before occlusion of the aneurysm”; however, the guidelines do not specify the type of laxatives.⁹

This study was performed to assess the relationship between developing loose stool (i.e., diarrhea) and DIND, as well as describing the pattern of laxative use at a single, large neurosurgical center in the United Kingdom.

Methods

Patient Selection

All adult patients (> 16 years of age) admitted to the Department of Neurosurgery at Leeds General Infirmary, between August 2019 and September 2020, with a diagnosis of aSAH (confirmed by CTA or DSA with the findings corroborated by a consultant neuroradiologist) were included in the study. Patients presenting with SAH due to trauma, patients in whom no neurovascular lesion was identified, and patients for whom SAH was due to an alternate (nonaneurysmal) lesion were excluded from the study. Patients were initially identified using the UK and Ireland Subarachnoid Hemorrhage Database, and entries were then cross-checked with our local neurovascular database for completeness.

Data Collection

Data were collected from the hospital electronic patient records, prescribing and dispensing systems, and aforementioned databases. Data regarding diagnosis and development of vasospasm and DIND were collected alongside fundamental demographic information. Stool charts were assessed for the presence of diarrhea during the admission. Episodes of hyponatremia, the prescription of laxatives, duration of critical care unit stay, and the total inpatient length of stay (LOS) were also recorded.

Definitions

Diarrhea was defined as type 6 or 7 on the Bristol stool chart.¹⁰ In line with our local biochemistry reference range, hyponatremia was defined as a laboratory serum level ≤ 133 mmol/L with or without clinical symptoms. Our cases were defined as patients with DIND who had diarrhea within 3 days prior to the onset of DIND. Our

controls were defined as patients who did not exhibit features of DIND and who had diarrhea within 21 days of admission (to reflect the expected time frame of DIND onset).

Standard Practice

It is part of the standard aSAH protocol at our institution that all patients are prescribed laxatives (usually lactulose and senna) on admission in order to prevent straining and counter the effects of opiate analgesia. Patients are also given a target 3-L fluid intake, unless contraindicated, which can be managed orally if the patient is able, or, more commonly, with 0.9% NaCl intravenous fluid infusions.

Statistical Analysis

Odds ratio analysis and standard t-test statistical analysis were performed, and the significance level was set at $p \leq 0.05$.

Results

Patient Demographics

A total of 105 patients were included, 62% of whom were female, with a mean and median age of 54 years (range 24–84 years). Diarrhea was noted in 12 patients (11.4%), 58% of whom subsequently developed DIND. Of the 93 patients who did not have diarrhea, 8 (8.6%) went on to develop DIND (OR 15.30, CI 3.92–59.14; $p = 0.0001$). All 105 patients were prescribed laxative agents, with 3 patients receiving 1 agent, 30 receiving 2 agents, 62 receiving 3 agents, 8 receiving 4 agents, and 2 patients receiving 5 agents (including enemas).

When patients who developed diarrhea and those who did not were compared, there was no significant difference observed with regard to sex (50% vs 37% male, $p = 0.3810$), age (mean 55 years vs 54 years, $p = 0.839$), or modified Fisher grade ($p = 0.314$) (Table 1). There was, however, a significantly increased proportion of poor World Federation of Neurosurgical Societies grades (grade IV or V) noted in the diarrhea group ($p = 0.005$).

Hyponatremia

There was no association between hyponatremia and diarrhea (OR 1.28, CI 0.3776–4.3491; $p = 0.691$). A total of 39 patients (37%) developed hyponatremia (the lowest serum values ranged from 122 to 133 mmol/L with a mean of 128.5 mmol/L), with the mean day of onset being day 7 postictus. Of these 39 patients, all received NaCl fluids intravenously, all received slow sodium, and 16 patients (41%) received fludrocortisone treatment.

Discussion

Patients with aSAH who develop diarrhea have significantly increased odds of developing DIND. Diarrhea can have a number of causes, such as medication and gastrointestinal disease. Given that 100% of patients were prescribed a laxative agent, with 97% being prescribed more than 2 laxative agents, this may represent a potential preventable cause of excessive fluid loss and potentially of DIND as well. Therefore, in patients with aSAH,

TABLE 1. Demographics of patients with and without diarrhea

Characteristic	Diarrhea (n = 12)	No Diarrhea (n = 93)	p Value
Mean age, yrs (range)	55 (40–72)	54 (24–84)	0.839
Sex, n			0.381
M	6	34	
F	6	59	
Modified Fisher grade, n			0.314
1	0	7	
2	1	12	
3	4	42	
4	7	32	
WFNS grade, n			0.005
I	2	49	
II	2	21	
III	0	0	
IV	3	7	
V	5	16	
Treatment, n			<0.005
Endovascular	12	86	
Microsurgical	0	7	

WFNS = World Federation of Neurosurgical Societies.

cautious laxative prescriptions should be considered, and gastrointestinal fluid loss from diarrhea should be noted and replaced appropriately, with reversible causes being addressed.

Patients cared for in level II and III environments frequently experience constipation;⁴ hence, we should not necessarily expect aSAH patients to develop diarrhea. All the patients who had both diarrhea and DIND in this study were prescribed laxatives. At the time of DIND diagnosis and diarrhea onset, all patients had a secured aneurysm.

Osmotic laxatives are commonly used laxative agents, although there are alternatives available with different mechanisms of action, such as bulking agents, fecal softeners, and bowel stimulants.⁵ Several new agents that target different mechanisms also appear promising, such as chloride-channel activator (lubiprostone), guanylate cyclase agonist (linaclotide), serotonin 5-hydroxytryptamine receptor 4 agonist (prucalopride), and peripherally acting mu-opioid receptor antagonists (alvimopan and methylnaltrexone) for opioid-induced constipation. Drugs such as methylnaltrexone bromide are opiate antagonists with limited ability to cross the blood-brain barrier due to their quaternary amine structure; therefore, they reduce peripheral opioid-related adverse effects when administered with opiates.⁵ The National Institute for Health and Care Excellence has been unable to make a national recommendation for methylnaltrexone use in the National Health Service (NHS), preventing use within NHS hospitals; currently, opioid receptor antagonist use is restricted to opioid-induced constipation failing other laxative therapies and for palliative care patients.¹¹

It has been established that early (< 24 hours) treatment of ruptured intracranial aneurysms is associated with im-

proved clinical outcome,¹² and most neurosurgical departments will aim to secure a ruptured aneurysm as promptly as possible. Given that the interval between admission to the neurosurgical department and a ruptured aneurysm being secured is typically brief, it might be argued that any laxative use during this time is unlikely to offer substantial benefit, in terms of the prevention of pretreatment rebleeding.

Patients who developed diarrhea had an increased mean LOS in the high-dependency or intensive care units (19 days vs 7 days, $p = 0.002$) and increased LOS overall (34 days vs 17 days, $p = 0.015$). The national average cost of stay at a level II or higher (high-dependency unit or higher) care facility is £1394.50,¹³ and, thus, the cost of level II or higher care for those with aSAH and diarrhea is estimated to be an average £26,495.50 per patient compared with £9761.50 per patient for those who did not develop diarrhea.

Limitations

This study has only been performed at a single institution where the standard protocol is to prescribe laxatives on admission to all patients with aSAH. This is a primary study and should be expanded to multiple centers.

Conclusions

It is possible that indiscriminate laxative prescription may increase gastrointestinal fluid loss in patients with aSAH. This potentially unnecessary laxative use may result in iatrogenic diarrhea in this patient cohort, which, in turn, may increase the risk of patients developing DIND. It is crucial that gastrointestinal fluid loss is accounted for as part of the fluid-balance assessments for these patients, and that every effort is made to avoid preventable causes of excessive fluid loss, including cautious prescription of laxatives in patients with aSAH. Therefore, laxative prescriptions (including the type of laxative) should be carefully considered. The avoidance of unnecessary laxative prescriptions may not only improve clinical care but also have benefits from a financial and critical care, bed capacity perspective.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Gelder. Acquisition of data: Gelder, Bautista, Awan. Analysis and interpretation of data: Gelder, Bautista. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: Gelder. Approved the final version of the manuscript on behalf of all authors: Gelder. Statistical analysis: Bautista. Administrative/technical/material support: Gelder, Anderson. Study supervision: Anderson.

Supplemental Information

Videos

Video Abstract. <https://vimeo.com/675884802>.

Correspondence

Chloé Louise Gelder: Leeds General Infirmary, Leeds, United Kingdom. chloegelder@nhs.net.