Title and Abstract

Title

Sodium After Subarachnoid Haemorrhage: a national prospective multi-centre audit of the management of hyponatraemia following spontaneous subarachnoid haemorrhage in the United Kingdom and Ireland (SASH)

Abstract

Background: Subarachnoid haemorrhage (SAH) is an acute neurosurgical condition affecting around 6-12 persons per 100,000 population in the UK each year.[1] Reported rates of hyponatraemia following spontaneous SAH range from 19%–56%.[2–4] Hyponatraemia has been associated with an increased risk of seizures, neurological deficit, length of hospital stay and mortality.[5] Guidelines for the monitoring and management of hyponatraemia in the general hospital population have been produced[6–8], but it is not clear if these are followed or are appropriate following SAH or whether patient outcomes are affected by different approaches to monitoring, investigation, and treatment of hyponatraemia.

Aims: Our primary aim is to audit the monitoring, investigation and management of hyponatraemia following SAH against current guidelines. We will also: 1) establish the UK incidence of hyponatraemia following SAH; 2) identify risk factors for hyponatraemia following SAH; 2) describe the temporal course of serum sodium fluctuation following SAH; 3) determine the effect of hyponatraemia and its management on patient outcomes.

Methods: All adult patients with spontaneous SAH admitted to neurosurgical units (NSUs) in the UK and Ireland over a two-month period will be eligible. Patients with traumatic SAH will be excluded. Anonymised data will be collected via a secure online database. Adherence to standards for investigation and monitoring of hyponatraemia will be assessed. The frequency and time course of hyponatraemia following SAH will be described. Risk factors for developing hyponatraemia will be assessed and any association between hyponatraemia and its management on patient outcome will be investigated.

Conclusion: Assessing the investigation and management of hyponatraemia following SAH will describe current practice and identify any associations between variation in practice and outcomes. We will provide baseline data to design strategies to prevent or manage hyponatraemia following SAH to facilitate the best possible patient outcomes.

Steering Committee

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Introduction

Background/Rationale

Subarachnoid haemorrhage (SAH) is an acute neurosurgical condition affecting around 6-12 persons per 100,000 population in the UK each year[1]. Hyponatraemia affects 20-30% of the general hospital population[9,10] and complicates 19%–56%[2–4] of cases of SAH. Patients with SAH are believed to be at high risk of hyponatraemia as a consequence of the syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt wasting syndrome (CSW), critical illness, high volume intravenous fluid supplementation to reduce risk of or treat vasospasm, and vomiting[4,5,11].

In the general hospital population, hyponatraemia is associated with increased risk of seizures, length of hospital stay and mortality[9,12–14]. As SAH is typically associated with raised cerebral metabolic rate and reduced cerebral blood flow, these patients are particularly vulnerable to cerebral perfusion-metabolism mismatch[15,16], which hyponatraemia may exacerbate by increasing neuronal excitability[17]. Hyponatraemia has been reported to be associated with increased risk of cerebral arterial vasospasm causing delayed cerebral ischaemia[18]. Recently, a large systematic review[5] suggested that although hyponatraemia alone following SAH was not

associated with mortality, it was independently associated with increased risk of delayed cerebral ischaemia and length of hospital stay. Increased length of time in requiring acute management of hyponatraemia might delay mobilisation and rehabilitation interventions[19]. Other authors have suggested that fluctuations in sodium are more clinically significant than absolute hyponatraemia[20,21]. Moreover, inappropriate rapid correction risks further neurological deficit due to central pontine myelinolysis[22,23].

Despite being the most commonly detected electrolyte abnormality occurring in SAH patients[3], no national guidelines have been developed which directly address the management of hyponatremia following SAH. Furthermore, although many studies indicate a link between hyponatremia and generally poorer outcomes, the specific impact remains unclear, with wide variation and inconsistent findings for individual outcome measures between studies. This may be due to the small sample sizes in studies conducted to date, with the majority including fewer than 100 patients [4,24,25] and the largest 298 patients[2]. It may also reflect a real variation in detection or treatment of hyponatraemia following SAH as a consequence of a lack of dedicated clinical guidelines. Management options reported in the literature include sodium supplementation, fluid restriction and the use of mineralocorticoid or glucocorticoid steroids[26–28]. Unfortunately, a lack of unbiased, large-scale studies using homogenous outcome measures[29] has made it difficult to introduce effective quality improvement initiatives at a national scale, identify correlations between management and outcome, or design pragmatic randomised controlled trials. The wide variation in reported screening and treatment options for hyponatraemia after SAH may be symptomatic of variation in clinical practices. To establish a national baseline, we therefore propose a UK wide, hospital-based audit of screening, investigation and management of hyponatraemia following SAH.

Objectives

Primary Aim

1. To determine if the current UK management of patients with SAH adhere to European Stroke Organisation guidelines[8] for electrolyte monitoring after SAH and the European Society of Endocrinology guidelines[6] for investigation of hyponatraemia?

Secondary Aims

2. Identify the proportion of patients develop hyponatraemia following spontaneous SAH?
3. Establish the early time course of sodium fluctuation following spontaneous SAH?
4. Identify risk factors for hyponatraemia following spontaneous SAH?
5. Determine if hyponatraemia or choice of management strategy are associated with patient outcomes?

Audit Standard

On the basis of recommendations described in guidance by the European Stroke Organisation[8] and the European Society of Endocrinology[6] we propose the following audit standards:

For detection of hyponatraemia:

i) U&Es should be measured every 2 days minimum from diagnosis of SAH

For management of hyponatraemia (patients with low Na (<135) post-SAH):

i) Measure U&Es every 2 days minimum from diagnosis
ii) Assess daily volume status whilst hyponatraemic
iii) Measure (at least once)
    a. Blood glucose
    b. Urinary sodium
    c. Urinary osmolality
    d. Serum osmolality
    e. Morning cortisol

Methods

Study Design

A prospective national multi-centre audit of routinely collected patient data will be undertaken.

Setting

All adult NSUs in the UK and Ireland will be invited to participate in the audit. NSUs will be required to appoint a consultant or trainee as local coordinators who will register the audit as per local guidance and oversee its local undertaking. The audit will only be started in local NSUs once local audit approval and registration is in place.

Participants

All adult patients aged over 18 years admitted to participating neurosurgical units with spontaneous SAH during a 2-month period of October-November 2019 will be eligible for inclusion. Spontaneous SAH can be aneurysmal or non-aneurysmal. Patients with traumatic SAH will be excluded. All patients will be followed up to discharge from the NSU.

Inclusion criteria

- Adult patients (aged ≥ 18 years)
- Admission to a participating NSU between 1st September - 31st December 2019
- Diagnosis of spontaneous SAH confirmed by CT or lumbar puncture from any cause (including, but not limited to: aneurysmal, vascular malformation, non-aneurysmal)

Exclusion criteria

- Diagnosis of traumatic SAH
- Patients under 18 years of age
- Patients not admitted to a participating NSU
- Patients admitted to a participating NSU before 1st September or after 31st December 2019

Variables

The following variables will be collected through use of an online proforma and stored on a secure and encrypted central database using Castor EDC software[30]:

Baseline Characteristics	
Anonymised Patient ID	generated by software
Site recruited	categorical (all centres)
Age	continuous
Sex	dichotomous (M/F)
Weight	continuous
Height	continuous
Diabetes mellitus	dichotomous (Y/N)
Chronic kidney disease	dichotomous (Y/N)
Baseline eGFR (Pre-admission)	categorical (>90; 60-89; 59-45; 44-30; 29-15; <15)
Polycystic kidney disease	dichotomous (Y/N)
Heart failure	dichotomous (Y/N)
Adrenal insufficiency (primary or secondary)	dichotomous (Y/N)
Systemic glucocorticoids prescribed in the last 3 months	categorical (prednisolone/ dexamethasone/ methylprednisolone/ hydrocortisone/not recorded))
Hyponatraemia observed in biochemistry (over last year) prior to presentation	dichotomous (Y/N) No information
Antihypertensive treatment prior to admission	categorical (Tick boxes to allow for polypharmacy) (Diuretic/calcium channel antagonist/ACE inhibitor / ARB2 blocker/ beta blocker/ Other)
Other relevant preadmission medication	categorical (Tick boxes to allow for polypharmacy) (Antipsychotic/Antidepressant/Antiepileptic/PPI/ other)
Previous subarachnoid haemorrhage	dichotomous (Y/N)
GCS (Best post-resuscitation after hospital admission)	categorical (3-15 with EVM breakdown)

SAH Characteristics	
WFNS Grade	categorical (1-5)
Ictus to admission time	continuous (days and hours)
Modified Fisher Grade[31]	categorical (1-4)
Evidence of intraparenchymal haemorrhage	dichotomous (Y/N)
New focal neurological deficit (FND) at admission	dichotomous (Y/N)
Aneurysm/cause?	categorical (aneurysm, AVM, no vascular cause found, other)
Aneurysm/lesion location	categorical (MCA, ACA, ICA, Acomm, Pcomm, basilar, PCA, other (state))
Aneurysm/lesion management	categorical (Clipping, endovascular coiling, endovascular web device, other)

Monitoring and Management (Daily for each 24hrs) FOR ALL PATIENTS UNTIL DISCHARGE OR 21 DAYS	
Day	Day 0 (post-ictus), 1,2, 3… to 21 or discharge whichever occurs first
Na	Continuous (Time & Value) (not recorded tick box) Multiple entries per day, if recorded. If time not filled in, then treated as daily.
Total input (ml) [type & mLs for each]	categorical (Hartmann's/Ringer's lactate/plasmalyte; 0.9%NaCl; 1.8%NaCl; 3% NaCl; mannitol 10%, 5%, 20%; HAS; RCC; Oral intake) & continuous (mLs) (not recorded tick box) Multiple entries per day, if recorded
Total output (ml) [type & mLs for each]	categorical (Urine; Vomit; PR loss; CSF) & continuous (mLs) (not recorded tick box) Multiple entries per day, if recorded
BP 8am or closest morning measurement	Systolic / diastolic
Heart rate 8am or closest morning measurement	continuous
Documented aim for fluid input	continuous (mLs/24hrs) None documented
Urea	continuous
Hematocrit	continuous
Given nimodipine	dichotomous (Y/N)
Newly prescribed antihypertensive	categorical (diuretic, calcium channel antagonist, other (specify))
Seizures in past 24h	dichotomous (Y/N)
Vomiting in past 24h	dichotomous (Y/N)

Only for those with Na <135 (diagnosis of hyponatraemia)	
Sodium (Urine)	Continuous Not tested today
Osmolality (Plasma)	Continuous

	Not tested today
Osmolality (Urine)	Continuous Not tested today
Glucose	Continuous Not tested today
Morning cortisol	continuous
Time of morning cortisol sample	continuous (24-hour clock)
Synacthen stimulated cortisol	continuous
Time since Synacthen	dichotomous (30min/60min)
TSH	Continuous Not tested today
Free T4	Continuous Not tested today
Volume assessment performed?	categorical (CVP, fluid balance, clinical, not assessed)
Volume assessment today	categorical (Hypervolaemic, euvolaemic, hypovolaemic, not documented)
Treatment of hyponatreamia today (tick boxes and extra information)	None Hypertonic saline – % and amount Slow sodium – no of tablets, frequency Fluid restriction (this may occur later in course) Tolvaptan (dose frequency) Demeclocycline (dose frequency) Loop diuretic- usually prescribed with slow sodium (dose frequency) Urea tablets Other
Cause for hyponatraemia stated in notes	categorical (CSW, SIADH, Adrenal insufficiency, intravascular depletion, none, other (text)) ('clinicians disagree' tick box)
Endocrinologist contacted	Telephone consultation today Review today Not today

Outcomes	
Length of Stay (LOS) (measured at discharge for all patients (even if LoS >21 days)	
Total LOS in NSU (days) (including HDU/ITU)	continuous
HDU / ITU admission?	HDU, ITU, none
LOS in HDU (days)	continuous
No of HDU admissions	continuous
LOS in ITU (days)	continuous
Number of ITU admissions	continuous
Discharge destination	categorical (Home independent, home with live in carer, home with formal package of care, other secondary care hospital, neurorehabilitation unit, general rehabilitation unit, nursing home, sheltered accommodation)
Is discharge destination same as prior to SAH?	Yes No
Morbidity & Mortality (measured at discharge)	
Modified-Rankin scale (mRS) at discharge from NSU	categorical (0-6)
New FND at discharge from NSU	dichotomous (Y/N)
Other morbidity in NSU	text

Hydrocephalus (at any point during admission)	On imaging, no action required Required LP Required lumbar drain Required EVD/VAD
Evidence of vasospasm (at any point during admission)	categorical (on Doppler only, no clinical effects on CTA only, no clinical effects clinical deficit, vascular imaging normal clinical deficit, vasospasm on imaging, clinical only)
Ventriculitis (at any point during admission)	dichotomous (Y/N)
Mortality	dichotomous (Y/N)
If mortality: day of admission?	continuous
Sodium at discharge	continuous
Treatment for hyponatraemia on discharge	categorical (Slow sodium/tolvaptan/demeclocycline/other)

The WFNS scale grades SAH severity based on the GCS and the presence of focal neurological deficits. The Modified Fisher grade predicts risk of cerebral vasospasm and clinical outcome in patients post-SAH, by stratifying severity based on volume of hemorrhage seen on CT imaging[31]. The Modified-Rankin scale (mRS) is a functional outcome measure assessing degree of disability and/or dependence of patients at discharge. It has been widely used and has established validity and reliability[32].

Data Sources/ Measurement

Data collection will initially be piloted in one unit (Edinburgh). Medical student data collectors will extract the relevant routinely collected data (outlined above) from patient electronic and paper notes under supervision by a local site neurosurgical trainees and/or consultant. Cases will be identified from ward staff, daily on-call teams, on-call logbooks, post-call handovers and radiology meetings.

A detailed study guide will be provided to assist data collectors. Online training webinars will be carried out to familiarise data collectors with data collection forms and audit background.

Study Size

Assuming a conservative incidence of 8 cases of SAH per 100,000 population, it is assumed that 5,600 cases occur nationally per year (combined UK and RoI population = 70 million). If 80% of patients over a two-month period could be captured, an estimated 760 cases could be studied.

Statistical Methods

We will determine and report the number and percentage of cases meeting each audit standard.

Hyponatraemia will be defined based on guidance from the European Society of Endocrinology[6] detailed below. An identified case of hyponatraemia will be defined as any patient admission with at least one episode of hyponatraemia during the first 21 days following a diagnosed SAH.

Severity	
mild	a serum sodium concentration between 130 and 135 mmol/L
moderate	a serum sodium concentration between 125 and 129 mmol/L
profound	a serum sodium concentration less than 125 mmol/L
Temporality	
acute	an episode of hyponatraemia lasting less than 48 hours
chronic	an episode of hyponatraemia lasting greater than 48 hours

Baseline characteristics for both hyponatraemic and non-hyponatraemic groups will be described using number and percentage, or median and interquartile range (IQR).

Incidence of hyponatraemia will be calculated based on catchment populations. Differences between baseline and SAH characteristics of patients who develop hyponatraemia and those who do not will be tested for statistical significance in univariable analyses using parametric and non-parametric tests of continuous and categorical data, as appropriate. Cox regression will be undertaken to assess time to onset of hyponatraemia. Sensitivity analyses will be undertaken to consider competing risk of mortality. Association between mRS and hyponatraemia will be undertaken using logistic regression. Both models will be fit to potential covariables selected *a priori* in an exploratory stepwise fashion.

Fluctuation of sodium will be assessed in 24 hourly increments by calculating area under the curve (AUC) for plasma sodium deviation from admission, daily plasma sodium difference from normal (defined as 140mmol/L) and daily plasma sodium difference from previous day's mean plasma sodium concentration. Absolute differences from these reference points will also be calculated. Where documented, ultradian variance will also be assessed.

Anticipated Outputs

On completion of the study, the data will be analysed and a report will be prepared. The study report will be submitted for publication in an open access peer-reviewed journal and presented at scientific meetings.

Authorship/Collaborator Status

Authorship will be credited to the Steering Committee, who have designed, run, and analysed this study. Additional collaborators may be co-opted into the writing group following significant contributions to study design, data collection, data analysis, and writing of the study report, at the discretion of the steering committee.

All consultants, trainees, or medical students contributing to data collection will receive credit with collaborator status on all publications.

Data Management

Anonymous data will be entered into a study specific secure database hosted by Castor EDC[30] will be entered directly into the electronic database from patient notes and charts using the participant's unique study number. This study number is assigned on creating a new patient record in the database. The clinical team can only view the records of patients from their own centre. A local spreadsheet that links the participant's unique study number to their personal details will be kept on an NHS computer restricted with user names and passwords to allow the follow up data for each participant to be entered. Published results will not contain any personal data that could allow identification of individual participants.

Ownership of the complete dataset arising from this study resides with the steering committee. Local data collected as part of this study belongs to the local team collecting that data. Summaries of results will be made available to investigators. Following the initial analysis and publication, study data will be made available to those who submit successful peer-reviewed proposals for use of the data to the steering committee.

Castor EDC is ISO27001, ISO 27002 and NEN7510 certified. It fully complies with all applicable laws and regulations: Good Clinical Practice (GCP), 21 CFR Part 11, EU Annex 11, and the European Data and privacy laws, including General Data Protection Regulation (GDPR).

Registration

The protocol will be reviewed by the NSAMR and BNTRC committees and submitted for peer review publication. All NSUs will register the audit locally and will only begin local data collection once audit approval is in place.

Conclusions

Conclusion

Assessing the investigation and management of hyponatraemia following SAH will describe current practice and identify any associations between variation in practice and outcomes. We will provide baseline data to design strategies to prevent or manage hyponatraemia following SAH to facilitate the best possible patient outcomes.

Proposed Timeline

Activity	Apr 19	May 19	June 19	July 19	Aug 19	Sept 19	Oct 19	Nov 19	Dec 19	Jan 20	Feb 20	Mar 20	Apr 20	May 20
Design, set up & registration														
Student & hospital recruitment														
Training of data collectors														
Data collection & local submission														
Data analysis & writing of outputs														
Result dissemination														

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Appendix

WFNS classification	Description
Grade 1	GCS 15; no motor deficit
Grade 2	GCS 13-14; no motor deficit
Grade 3	GCS 13-14; with focal neurological deficit
Grade 4	GCS 7-12; with or without deficit
Grade 5	GCS <7; with or without deficit

Modified Fisher classification[31]	Description
Grade 0	No subarachnoid haemorrhage (LP diagnosis)
Grade 1	Focal or diffuse thin SAH, no IVH
Grade 2	Focal or diffuse thin SAH, with IVH
Grade 3	Thick SAH present, no IVH
Grade 4	Thick SAH present, with IVH

mRS score	Description
0	Asymptomatic
1	Some symptoms, but no significant disability; able to carry out all usual activities
2	Slight disability; able to look after own affairs without assistance but unable to carry out all previous activities
3	Moderate disability; requires some assistance for activities but able to walk unassisted
4	Moderately severe disability; unable to attend to own bodily needs, or walk, without assistance
5	Severe disability requiring constant nursing; bedridden; incontinent
6	Dead