Impact of Hyponatremia on Morbidity, Mortality, and Complications After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review

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Key words
- Cerebral salt wasting syndrome
- Hemorrhagic stroke
- Hyponatremia
- syndrome of inappropriate anti-diuretic hormone secretion
- Subarachnoid hemorrhage

Abbreviations and Acronyms
DIND: Delayed ischemic neurologic deficit
GOS: Glasgow Outcomes Scale
HH: Hunt and Hess
ICH: Intracerebral hemorrhage
ICU: Intensive care unit
mRS: Modified Rankin Scale
OR: Odds ratio
SAH: Subarachnoid hemorrhage
WFNS: World Federation of Neurosurgical Societies

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BACKGROUND: **Hyponatremia is a common metabolic disturbance after aneurysmal subarachnoid hemorrhage (SAH), and it may worsen outcomes. This review aims to characterize the effect of hyponatremia on morbidity and mortality after SAH.**

OBJECTIVES: **We sought to determine the prevalence of hyponatremia after SAH, including in subgroups, as well as its effect on mortality and certain outcome measures, including degree of disability and duration of hospitalization.**

METHODS: **A search of terms "hyponatremia" and "subarachnoid hemorrhage" was performed on PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. Studies were included if they reported prevalence of hyponatremia and if they discussed outcomes such as mortality, duration of stay, functional outcomes (e.g., Glasgow Outcomes Scale), or incidence of complications in patients with aneurysmal SAH. Two independent researchers assessed the titles and abstracts and reviewed articles for inclusion.**

RESULTS: **Thirteen studies met inclusion criteria. The prevalence of at least mild hyponatremia was 859 of 2387 (36%) of patients. Hyponatremia was associated with vasospasm and duration of hospitalization, but it did not influence mortality.**

CONCLUSION: **Hyponatremia is common after SAH, and there is evidence that it is associated with certain poorer outcomes. Larger, prospective studies are needed to assess these findings and provide further evidence.**

INTRODUCTION

Nontraumatic subarachnoid hemorrhage (SAH) caused by aneurysm rupture affects up to 30,000 people each year, and its high mortality of up to 50% may be attributable to the initial bleed or complications such as rebleeding or vasospasm.[1-3] Hyponatremia is a common finding in patients with SAH, with some studies reporting a prevalence of more than 50% of patients.[4,5] This electrolyte disturbance is associated with various neurologic manifestations, including altered mental status, seizures, and coma, which are related to the physiological role of sodium as a major extracellular cation.

In the setting of hypo-osmolar hyponatremia, the abnormal osmotic balance causes a fluid shift from plasma to the interstitial fluid, causing intracellular edema and impaired cellular function.[6-9] Although concerning symptoms such as cerebral edema and intracranial hypertension occur with severe hyponatremia (<125 mEq/L) or acute decreases in serum sodium, mild, chronic hyponatremia also has been associated with neurological injury.[10,11]

The treatment of hyponatremia frequently is a challenge because of its varying, often clinically overlapping etiologies, which have different treatments. Furthermore, inappropriate management may significantly worsen the patient's clinical status—for example, classically, rapid correction of hyponatremia may lead to central pontine myelinolysis.[12] Common causes of hyponatremia in the general public include congestive heart failure, cirrhosis, and diuretic use, but after SAH, syndrome of inappropriate anti-diuretic hormone secretion (SIADH) and cerebral salt wasting syndrome (CSWS) are the preeminent etiologies.[13] Whereas SIADH is a euvolemic state characterized by excess free-water retention, CSWS is a result of salt and water loss caused by inappropriate levels of natriuretic peptides.[14] The differences in management, most notably, are fluid restriction in SIADH and fluid administration in CSWS.[15]

Although once thought to be an innocent bystander in other conditions, hyponatremia has been shown recently to have an effect on mortality in cardiovascular disease, pulmonary infections, ischemic stroke, and intracerebral hemorrhage (ICH).[16-21] For this reason, we sought to determine its effect on outcomes in patients with SAH.

The focus of this review addresses several key questions. First, we sought to

determine the overall incidence of hyponatremia in patients with aneurysmal SAH. We then determined whether certain subgroups are more susceptible to developing hyponatremia. Finally, we analyzed studies that examined effects of hyponatremia on outcomes such as mortality, length of hospital stay, functional outcomes, and in-hospital complications.

METHODS

An electronic search was conducted using the PubMed, CENTRAL, MEDLINE, and EMBASE for studies reporting the prevalence of hyponatremia and its associated clinical outcomes in patients with nontraumatic, aneurysmal SAH. The key words "subarachnoid hemorrhage" and "hyponatremia" were combined using 'and' for searching relevant studies.

To determine the prevalence and clinical significance on outcomes, studies were included if the following criteria were fulfilled: (1) Prevalence and/or incidence data on patients with hyponatremia and nontraumatic aneurysmal SAH; (2) studies that reported at least one of the following outcomes: mortality, duration of hospital stay, functional outcomes (e.g., Glasgow Outcomes Scale [GOS]), and complications. Studies that included SAH resulting from trauma, vascular malformations, or other nonaneurysmal causes were excluded. Other exclusion criteria were editorials, articles that did not have a version in English, or articles for which the full manuscript was not accessible via Columbia University servers.

Two independent reviewers screened the titles and abstracts manually. Studies that both reviewers agreed met inclusion criteria were added for review. Each reviewer examined the text, figures, and tables of the eligible and accessible full-text articles and extracted the following data: SAH etiology, study type, sodium cutoff used, overall prevalence of hyponatremia, number of patients with SIADH, and outcomes of the study. Data extracted for the purpose of calculating prevalence was compiled onto **Table 2**.

RESULTS

The selection of studies is outlined in **Figure 1**. The initial search yielded 418 articles with duplicates removed. Articles that met exclusion criteria were removed, yielding 171 articles on MEDLINE, CENTRAL, and EMBASE including 13 non-MEDLINE PubMed articles. After reviewing titles and abstracts of the remaining articles, 13 met full inclusion criteria and discussed the outcomes listed in our objectives.

Of the 13 studies, 9 were retrospective, 1 was a retrospective analysis of prospective data,[22] and 3 were prospective. Twelve articles defined hyponatremia as sodium <135 mEq/L (3 of which also used a lower sodium cutoff (<130 mEq/L) for the purposes of a subgroup analysis), and one exclusively used a lower cutoff of <130 mEq/L. One study[5] had a more recent post-hoc analysis,[23] but the results and discussion of the latter focused on other neurosurgical conditions other than SAH.

Overall, the proportion of patients with at least mild hyponatremia (Na <135 mEq/L) was 859 of 2387 (36%). Among the data available on patients with more significant hyponatremia (Na <130 mEq/L), the prevalence was 216 of 1357 (15.9%). **Table 1** outlines the general characteristics and outcomes of each study, each of which assessed at least one of the following outcomes: mortality, functional outcomes measured by clinical scales, in-hospital complications, and duration of hospital or intensive care unit (ICU) stay. **Table 2** details the findings of each study.

DISCUSSION

From this review, we identified 13 articles in which the authors assessed the impact of hyponatremia on SAH outcomes. We discuss the results of these studies, details of study design, and outcomes in specific subgroups.

Definition of Hyponatremia

A significant variation in study design was the definition of hyponatremia. Generally, hyponatremia refers to a sodium level less than 135 mEq/L, but, as with many electrolytes, clinically significant effects worsen

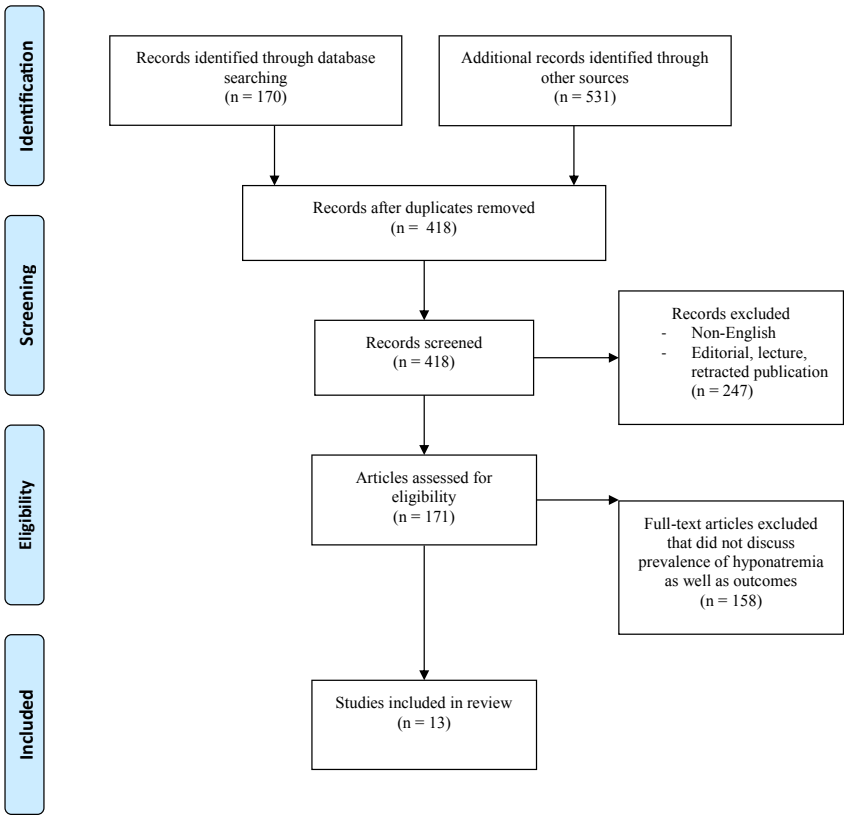

Figure 1. Flow chart showing retrieval process of full text articles identified on PubMed for inclusion into the systematic review. The same process was performed on CENTRAL, MEDLINE, and EMBASE.