OXFORD

Journal of Surgical Protocols and Research Methodologies, 2023, **3**, 1–5
https://doi.org/10.1093/jsprm/snad007
Study Protocol

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Neuroendocrine-induced hyponatremia in patients with traumatic brain injury: a systematic review and meta-analysis of the epidemiology, factors and prognosis

Emmanuel Chileshe Phiri[1,*], Tamara Tango[2], Tunde A. Olobatoke[3], Bhavya Ratan Maroo[4], Racheal Mpokota[5], Wesley Harrisson Bouche Djatche[6], Emmanuel Mukambo[7], Ugwoke Franklin Chiazo[8], Nathan Mugenyi[9], Emmanuel Mduma[10], Victor Meza Kyaruzi[11], Emnet Tesfaye Shimber[12], Fortune G. Gankpe[13], Ignatius Esene[14] and Getaw Hassen[15]

[1]Faculty of Medicine, Copperbelt University Micheal Chilufya Sata School of Medicine, P. O Box 71191, Ndola, Zambia
[2]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[3]College of Medicine, University of Lagos, Lagos State, Lagos, Nigeria
[4]Maulana Azad Medical College, New Delhi, India
[5]Faculty of Medicine, Levy Mwanawasa Medical University, P.O Box: 33991, Lusaka, Zambia
[6]School of International Education, Shanxi Medical University, Taiyuan, China
[7]Faculty of Medicine, Copperbelt University Micheal Chilufya Sata School of Medicine, P.O Box 71191, Ndola, Zambia
[8]Faculty of Medicine, University of Calabar, Calabar, Nigeria
[9]Faculty of Medicine, Mbarara University of Science and Technology, P.O Box 1410, Mbarara,Uganda
[10]Department of Oncology, Rabininsia Memorial Hospital, P.O BOX 67497, Dar es Salaam, Tanzania
[11]Department of Surgery, School of Medicine, Muhimbili University of Health and Allied Sciences, P.O.Box 65001, Dar es Salaam, Tanzania
[12]Emnet Tesfaye, School of Medicine, Hawassa University, P.O.Box 1560, Addis Ababa, Ethiopia
[13]CNHU HKM, Cotonou, Benin
[14]Division of Neurosurgery, Faculty of Health Sciences, University of Bamenda, Yaounde, Cameroon
[15]Department of Emergency Medicine, New York Medical College (NYMC), New York, NY, USA
*Correspondence address. Faculty of Medicine, Copperbelt University Micheal Chilufya Sata School of Medicine, P.O Box 71191, Ndola, Zambia.
Tel: (+260)764763158; E-mail: pschileshe24@gmail.com

Abstract

Traumatic brain injury (TBI) is a common brain dysfunction due to an external force as opposed to disease-induced brain damage. TBI is a leading global cause of high morbidity and mortality rates in the neurosurgical department. It contributes to ∼30% of deaths related to brain damage. A common complication of TBIs is hyponatremia secondary to neuroendocrine causes, including syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt wasting syndrome and adrenal insufficiency. Most recent studies suggest SIADH as the main cause of hyponatremia in TBI. This study aims to evaluate the effects of neuroendocrine-induced hyponatremia on the prognosis of TBI, demonstrate the epidemiology of hyponatremia in patients with TBI, assess all possible etiologies of hyponatremia in TBI, determine the prognostic outcomes of hyponatremia in TBI and determine the effect of hyponatremia on the prognosis of severe and moderate TBI. This study is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 guideline. A 10-year retrospective analysis of original published studies from January 2013 to January 2023 will be performed. This study will include the adult TBI patients (age ≥ 18 years old) who developed neuroendocrine-induced hyponatremia and original studies, randomized control trials, case controls, cohort studies and studies in English language. This study excludes the pediatric population and animal studies. For information sources, several electronic databases, including EMBASE, Pubmed, SCOPUS and Cochrane, will be searched. No ethical approval is required since the study does not involve human subject participation. However, the study findings will be applied for dissemination at scientific conferences and the manuscript will be submitted for publication to a reputable peer review journal. The research protocol is registered with PROSPERO registration No. CRD42023391854 and is available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023391854.

INTRODUCTION

Rationale

Traumatic brain injury (TBI) and illnesses, such as stroke and tuberculous meningitis, are often concomitant with electrolyte imbalances namely hyponatremia. Hyponatremia, a serum sodium level < 135 mmol/l, is the most common electrolyte abnormality in neurosurgical patients with TBI [1]. Previous studies have reported the incidence of hyponatremia in this patient group

Received: April 16, 2023. **Accepted:** April 25, 2023

to be ranging between 9.6 and 51%, with the condition being associated with poorer outcomes [2–4]. In addition, at least a third of all TBI cases are complicated by hyponatremia within 5 days following brain trauma [5]. Common etiologies of hyponatremia in TBI patients include neuroendocrine dysregulation syndromes like cerebral salt wasting syndrome (CSWS), syndrome of inappropriate antidiuretic hormone secretion (SIADH) and adrenal insufficiency (AI).

CSWS is defined as a renal loss of Na^+ following cranial injury, leading to hyponatremia with subsequent decreased extracellular fluid volume and low serum uric acid (normal serum uric acid = 250–750 mg/ 24 hours). While the pathophysiology of CSWS is not well understood, it is suspected that due to arterial stretch following a TBI, there is increased atrial natriuretic peptide, which has been associated as the leading cause of natriuresis and diuresis in CSWS.

Often times, most SIADHs are mistaken for CSWS because of their common factor 'hyponatremia'; however, the two show slight differences like SIADH being euvolemic (which is caused by electrolyte free water retention due to abnormal ADH release) and CSWS being hypovolemic due to renal salt loss leading to subsequent water loss. An important point to note is that CSWS can also be distinguished from renal causes of hyponatremia by inspecting the Na + urine concentration, which is elevated in CSWS than in renal causes of hyponatremia.

This electrolyte abnormality increases the risk of life-threatening secondary brain damage, such as cerebral edema, and has been previously associated with increased morbidity and mortality among TBI patients [6]. Proper diagnosis and management of neuroendocrine-induced hyponatremia remain a challenge in clinical practice, especially the differentiation between CSWS and SIADH. As these two conditions are corrected using opposite treatment strategies, misdiagnosis or confusion in the treatment regimen might exacerbate the hyponatremia and lead to severe complications. Further investigations remain necessary to provide up-to-date information on the incidence and prognostic factors in TBI patients with hyponatremia.

OBJECTIVES

General objective

- To evaluate the effects of neuroendocrine-induced hyponatremia on the prognosis of TBI.

Specific objectives

- To demonstrate the epidemiology of neuroendocrine-induced hyponatremia in patients with TBI.
- To assess factors associated with hyponatremia in TBI.
- To determine the prognostic outcomes of hyponatremia in moderate or severe TBI.

Participants

Adult (age ≥ 18 years old) TBI patients with neuroendocrine-induced hyponatremia (either SIADH, CSWS or AI).

Intervention/exposure

Hyponatremia (<135 mmol/l of sodium concentration in blood).

Comparators

Normonatremia versus hyponatremia.

Outcome

Prognosis (length of mechanical ventilation, length of ICU admission, overall survival and Glasgow outcome score (GOS)).

Study design

This is a systematic review- and meta-analysis-based study.

Research questions

- What is the incidence of neuroendocrine-induced hyponatremia in patients with TBI?
- What are the factors associated with neuroendocrine-induced hyponatremia among TBI patients?
- What is the effect of neuroendocrine-induced hyponatremia on the prognostic outcome among severe and moderate TBI patients?

METHODS

Protocol and registration

The protocol will be developed corresponding to guidelines by Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 and is registered to PROSPERO with Registration No. CRD42023391854 and is available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023391854.

Eligibility criteria

Inclusion criteria

The review study will include all original studies in English language, randomized control trial (RCT), cohort studies and case control studies that focus on the epidemiology, factors and prognostic outcomes of neuroendocrine-induced hyponatremia (i.e. SIADH, CSWS and AI) in adult patients (age ≥ 18 years old), with moderate or severe TBI within a space of 10 years retrospectively from January 2013 to January 2023.

Exclusion criteria

This study will exclude all studies based on animals, the pediatric population-based studies, case reports and any other articles not written in English language.

DATA SOURCES AND SEARCH STRATEGY

Information sources

The literature search will be conducted on the following databases: EMBASE, Pubmed, SCOPUS and Cochrane using the strategy constructed by application of predefined MeSH keywords and Boolean Operators. We will also trace back the relevant references in the included papers.

Search strategy

The following keywords were used in various permutations along with Boolean operator application: 'craniocerebral trauma' [MeSH Terms], 'head injuries, closed' [MeSH Terms], 'brain injury', 'brain trauma', 'traumatic brain injury', 'TBI', 'head injury', 'head trauma', 'SIADH', 'hyponatremia', 'cerebral salt wasting', 'CSW', 'adrenal insufficiency'.

PubMed search

For example, PubMed Strategy: ('craniocerebral trauma' [MeSH Terms] OR 'head injuries, Closed' [MeSH Terms] OR brain injury OR brain trauma OR traumatic brain injury OR TBI OR head injury OR head trauma) AND ('hyponatremia' [MeSH Terms] OR

hyponatremia OR SIADH OR cerebral salt wasting OR CSW OR adrenal insufficiency). These are included in the appendices as Supplementary Table A1.

Types of outcomes

The outcomes will be divided into primary and secondary outcomes.

Primary outcomes:

- Overall survival

Secondary outcomes:

- Number of stays in the ICU
- Number of days on mechanical ventilation
- GOS (i.e. disability (at final follow-up), etc.)
- Mortality
- Morbidity

Study selection

The review process will involve an initial screening of titles and abstracts of identified references by the three independent reviewers (Emmanuel Phiri, Tamara Tango and Victor Kyaruzi) using a blinded selection procedure. All reviewers will then evaluate the full text of potentially eligible studies to determine their eligibility for inclusion in the review. In cases of disagreement, consensus will be reached through discussion or by seeking the input of an additional author not part of the review team. The selection process will be recorded in a PRISMA flow diagram (Fig. 1) using Rayyan. Any key full text articles that are ultimately excluded from the review will be listed in a table of excluded study characteristics.

Data extraction and items

Data extraction will be conducted by two teams of independent reviewers (Tunde Olobatoke and Tamara Tango) using the Microsoft excel spreadsheet. An initial pilot data extraction will be carried out to ensure that the reviewers are familiar with the data being collected and the method and that everything is done homogeneously and correctly. The pilot will inform us of areas that need improvement and the appropriate changes will be implemented during the main data extraction. Afterward, the same reviewers will perform the main data extraction. At the end of the data extraction, the reviewers will meet to discuss differences in their decision, and if needed, a senior reviewer will be summoned to settle areas of conflict. The following data will be extracted from the main text of each of the eligible studies:

- **Study characteristics:** authors' name, year of publication, sample size, study design, country/location and length of follow-up.
- **Participant characteristics:** Sex, age, diagnosis (TBI with normotraemia or TBI with hyponatremia), causes of hyponatremia (AI, SIADH, etc.) significant history (e.g. history of hyponatremia), identified risk factors, severity of TBI (moderate or severe) using the GCS.
- **Diagnostic criteria:** This will include parameters such as the preoperative or baseline plasma and urinary sodium level and osmolality and the post-operative plasma and urinary sodium level and osmolality.
- **Outcomes:** Prognosis (mortality, disability, chance of recovery and recurrence)

Authors of the included studies will be contacted for any missing data via email or telephone call. If data cannot still be recovered after attempts to reach the author, all the reviewers will discuss and decide whether to include the study or not. Hyponatremia will be defined as serum sodium concentration of <135 mEq/l [7], although this value might vary in the different studies to be included. This will be accommodated as appropriate as long as proven methods were used for measurement. A GCS score between 9 and 13 will be considered as a moderate TBI, while a score between 3 and 8 will be considered as severe TBI [8].

Risk of bias in individual studies

Three reviewers (E.C.P., V.M.K. and T.T.) will independently assess the quality of studies to meet the criteria for inclusion by utilizing the Newcastle Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias (ROB) tool for RCTs. Only studies with a score of NOS ≥4 will be considered as low ROB and will be included for review and meta-analysis.

Data analysis

The extracted data will be imported into IBM SPSS version 26 [9] for statistical analysis. Studies characteristics such as authors' name, methodology, year of publication, outcomes, sample size and median period of follow-up of participants and prognosis will be recorded in tables. The relationship between the occurrence of TBI and hyponatremia will be considered to be statistically significant with a *P*-value of <0.05. Data will be synthesized for meta-analysis if the data collected from studies are homogenous and study participants are subjected to similar effects. The Joanna Briggs Institute approach [10] would be employed to synthesize data (incidence and prevalence score from each study included) to measure the proportion at 95% confidence interval and the overall incidence rate of hyponatremia in TBI patients.

For continuous data, mean no differences or standardized mean differences will be calculated, and for dichotomous data, odds ratios will be calculated. A random-effects model will be used to pool the data, and subgroup analyses will be conducted as appropriate.

Furthermore, for continuous categorical data, a simple logistic regression/tetrachoric analysis will be use to define the strength of the relationship between hyponatremia and TBI for variables that are statistically significant from the *P*-value.

Measurement of effect

We will pool and analyze data for both the hyponatremia and normonatremia groups. The risk ratio will be used to determine the relationship between each group and the prognosis of TBI. Similar analysis will be done for sub-groups as described above, but this will depend on the homogeneity of our data. For continuous and categorical variables, the mean difference or standard mean difference will be calculated, and the same applies for numerical variables.

ROB across studies

The publication bias will be analyzed and reported using the funnel plot for >10 articles included for meta-analysis.

Subgroup analysis

Generally, participants will be grouped into two; (i) TBI with normonatremia, and (ii) TBI with hyponatremia. The second group will be compared in subgroup analysis as follows:

- Severity of TBI: (moderate TBI GCS = 9–13) versus severe TBI (GCS = 3–8)

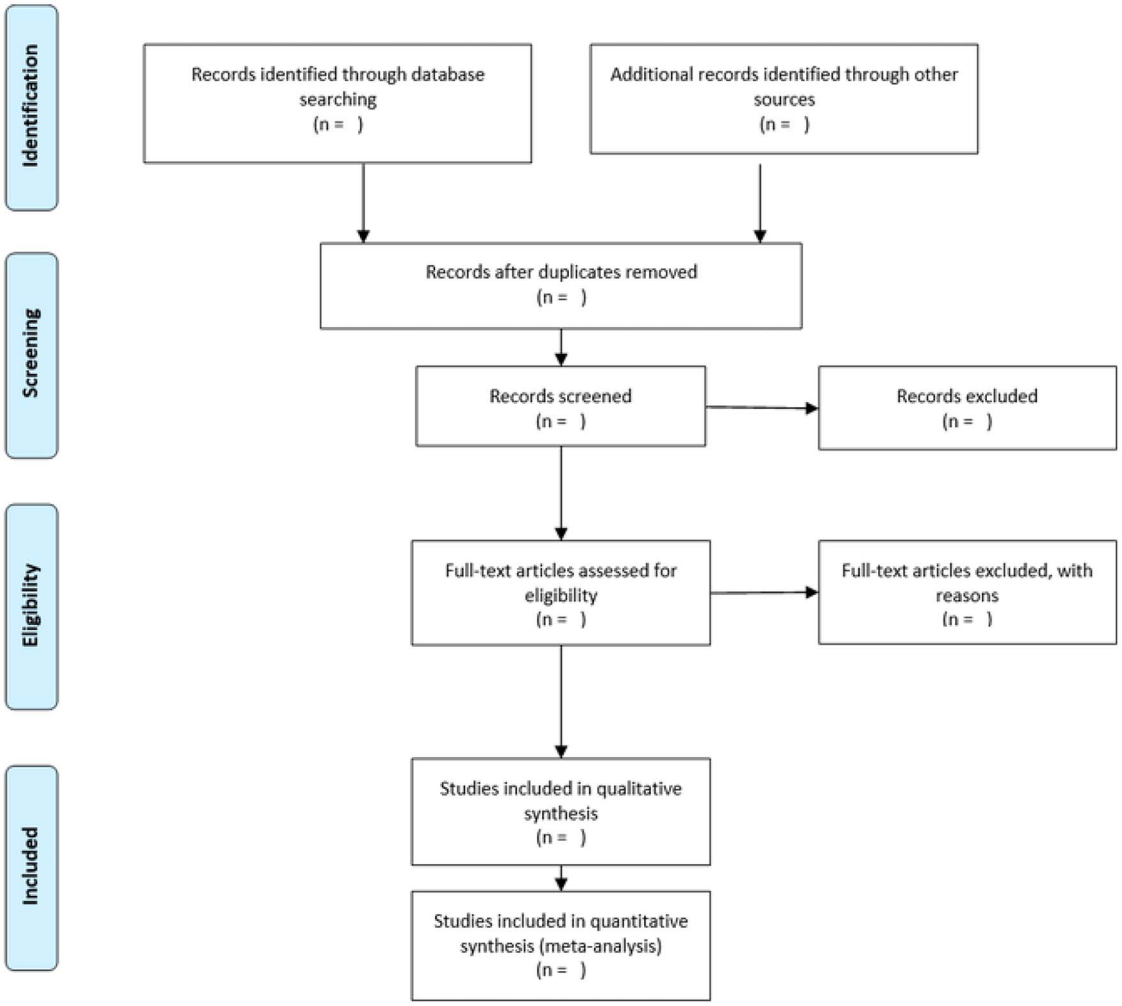

Figure 1. PRISMA flow diagram template shows a summary of the selection process from identification of papers to inclusion

- Patient's history: Participants with a history of hyponatremia versus those without a history of hyponatremia
- Outcome: Favorable versus unfavorable

Bivariate analysis would be conducted to find the relationship between the severity of TBI and hyponatremia. An history of hyponatremia will be considered as a significant risk factor for development of hyponatremia in TBI patient. A *P*-value of <0.05 will be considered to be statistically significant, and a Pearson correlation study will be done to determine the strength of this association.

EVALUATION OF HETEROGENEITY

The study's participants, methods and outcomes will be examined critically. Chi-squared and I^2 statistics will be used. Heterogeneity will be said to be present and statistically significant when the *P*-value is <0.05. Subsequently, an I^2 statistic value >50% will also be considered to be statistically significant.

Sensitivity analysis

If adequate data are found, a sensitivity analysis will be conducted to assess the robustness of the results. The sensitivity will be conducted by excluding all studies at high ROB, with unpublished data, and studies with missing data.

Strength of body of evidence

The strength of outcome and applicability of this review will be rated using GRADE guidelines and the overall validity of evidence will be scored as high, moderate, low and very low.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of Surgical Protocols and Research Methodologies* online.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL CONSIDERATION AND DISSEMINATION

No ethical approval is required since the study does not involve human subject participation. However, the study findings will be applied for dissemination at scientific conferences and the manuscript will be submitted for publication in a reputable peer review journal. The research protocol was registered with PROSPERO with registration number CRD42023391854.

AUTHORS' CONTRIBUTIONS

All authors took part in drafting the protocol and offered their expert opinion.

DATA AVAILABILITY

All materials regarding this study are available and shall be shared by the corresponding author upon reasonable request.

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