ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES

Prevalence, management and associated factors of severe and/or symptomatic hyponatremia using hourly-based, locally made, 3 % enteral table salt solution in resource limited settings.

Principal Investigator- Gadissa Birhanu (MD), Emergency Medicine and critical care Resident

Advisor- Dr. Demelash Gezahegne (MD), EMCC specialist
Dr. Bitania Debalkew (MD), EMCC specialist

Addis Ababa, Ethiopia, Dec 5 2024

Acknowledgements

Allow me to thank the following individuals and organizations for their valuable contributions to my research process.

First and foremost, my profound thanks go to my beloved mother, W/ro Asnakech Wedajo, for her endless love and support.

I also wish to acknowledge Addis Ababa University and the Tikur Anbessa Specialized Hospital Department of Emergency Medicine and Critical Care for the invaluable opportunity and project subsidy.

My heartfelt appreciation goes to my advisors for their guidance, encouragement, and unwavering support.

I would also like to express my gratitude to Dr. Merahi Kefyalew for his advice and encouragement during the research period.

Lastly, I thank my friend Mercy Habte for her technical assistance during the preparation of this thesis.

Acronym

AGE =Acute Gastroenteritis

AOR= Adjusted Odds Ratio

CLD= Chronic liver Disease

CI= confidence interval

DM=Diabetes mellitus

ED= Emergency department

EFMCA =Ethiopian food and medicine control authority

HIV= human immunodeficiency virus

IE= Infective Endocarditis

ICH=Intracranial hemorrhage

ICU= intensive care unit

IRB=Institutional Review Board

ISE=ion-selective electrode

IV= Intra-venous

IVC= Inferior vena cava

NaCl= sodium chloride

OR= odds ratio

PAD= Peripheral Arterial Disease

PCP =pneumocystis carinii pneumonia

POCUS= Point of care ultrasound

RCT= randomized control trial

SD= standard deviation

SIADH= Symptom of inappropriate antidiuretic hormone

SLE=Systemic Lupus Erythematosus

SPSS= Statistical Package for the Social Sciences

STG =standard treatment guideline

TASH= Tikur Anbessa specialized hospital

TB =Tuberculosis

TSP=tea spoon

VL= Visceral Leishmaniasis

Table of contents

Abstract

Background

Treatment of severe and acute hyponatremia is challenging in emergency departments of resource-limited setup.

Methods:

A single-center, cross-sectional retrospective study was conducted. We selected 148 patients from the emergency department using simple random sampling. Data were collected from laboratory results, patient charts, and electronic medical records (EMR) and analyzed using SPSS. Non-parametric tests, regression analysis, and Kaplan-Meier survival analysis were performed.

Result: From a total of 148 patients, 13(8.8%) were under-corrected, 99 patients (66.9%) achieved normal correction, and 36 patients (24.3%) were overcorrected. The Related-Samples Friedman's Two-Way Analysis of Variance by Ranks revealed a highly statistically significant (p-value=0.000) effectiveness in using a calculated dose of the locally made 3% enteral table salt solution for treating severe and/or acute hyponatremia in our study. The Independent-Samples Kruskal-Wallis Test showed that hypokalemia notably affected Day 1 serum sodium levels, causing greater variability ($p < .001$). Overcorrection was strongly associated with lower initial serum sodium levels (aOR=0.912, CI=0.860,0.966) and hypokalemia (OR=0.008, CI=0.002,0.031) and slightly associated with the total amount of the 3% solution administered on Day 1 (aOR=1.005, CI=1.001, 1.008). Undercorrection was significantly associated with the total amount of 3% solution taken on Day 1 (aOR=0.995, CI=0.0991, 0.998). Patients with undercorrection had a higher association with death (aOR=9.825, CI=1.927, 50.106). Osmotic Demyelination syndrome (ODS symptoms were associated with hypokalemia (aOR=6.929, CI=2.904,16.530), initial serum sodium level (aOR=0.933, CI=0.8810,0.987), and overcorrection (aOR=16.022, CI=6.194, 41.443). The Kaplan-Meier curve illustrated sharper increase for under-correction.

Conclusion and Recommendation

Using 3 % locally made enteral table salt solution is effective in treatment of severe and/acute hyponatremia management in resource limited setup. Calculating the solution using Edelman Equation is essential and effective for the management by reducing the risk of overcorrection. There was no association b/n the ODS symptoms and rate of death. There was no correlation between the principal diagnosis and comorbidities of patients who died. Undercorrection was the only statically significant component for the deaths in the study. We can consider giving a calculated locally made 3 % enteral table salt for patients with severe and/or acute hyponatremia management in resource limited setup where there are challenges in obtaining standard 3 % hypertonic solution. But a further and higher level of study is warranted, possibly an RCT that will compare our enteral table salt solution with the standard 3 % hypertonic solution.

List of Tables

List of Figures

Introduction

Sodium is the major extracellular cation. It has a magnificent role in muscle, nerves and cardiac cells for generation of action potential. The serum sodium level should be at equilibrium status. It is regulated by the renal and endocrine systems. [1] The normal serum sodium level ranges from 135-145. [2]

Hyponatremia is the lower serum level of sodium from the respective laboratory cut off point. The European clinical practice guideline suggests being less than 135 mmol/l. (3)

Hyponatremia is caused by the retention of water which will dilute the serum sodium and osmolality. The transcellular water shifts will be governed by the effective osmolality (tonicity). Sodium, its anions and glucose are the major particles that can affect the tonicity. But the general body osmolality can be affected by sodium, glucose and urea. [4,5]

But urea will not affect the effective osmolality (tonicity) it affect, due to its high cell membrane permeability. These make alcoholic and uremic patients at higher risk of cerebral edema. [4,5]

The prevalence of Hyponatremia in the emergency department is variable. It has been suggested, varying from 3% to 10%. [3,6,7,8] There are factors that can significantly affect the occurrence of hyponatremia in the emergency department (ED). Some of them are age, associated comorbidities, atmospheric condition and demography of local population. The prevalence of hyponatremia in elderly is high.[3,6,7,8] Evidence suggests that for patient greater than 80 years of age, the prevalence is about 17%, while for young age (16 to 21 years), it is 2%.
Comorbidities like acute or acute on chronic kidney disease also have high prevalence, which is estimated to be 30 %, from the normal population when they come to the ED. Seasonal variation of the atmospheric condition also affects this prevalence, where it is suggested being higher in hot periods. [3,6,7,8]

There are different ways to classify hyponatremia. One is based on the osmolality, as hypoosmolar, hyperosmolar and iso osmolar hyponatremia. [9] Based on the osmolality, hyponatremia can be classified into three, which are Hypoosmolar, hyperosmolar and iso osmolar. Clinically Hypoosmolar is the most important one. In which for sake of diagnosis and management it has three different sub classifications based on the volume status of the patient. [10]

The volume status of patients in the emergency department should be determined using the combination of clinical features, laboratory values, point of care ultrasound and passive leg raise. Presence of postural dizziness, postural rise in pulse rate which is more than 30 beats/minute, dry axilla and dry mucous membrane could be sign for hypovolemia in hyponatremia patient.[11] If the baseline values are available we can use the serum creatinine, urea and hemoglobin parameters for the volume status.[11] In Point of care ultrasound (POCUS) we can assess the

inferior vena cava (IVC) and determine the fluid status of patient.[12] But according to systemic reviews there is limited predictive ability of the IVC to determine fluid status.[13]

Hypovolemic hyponatremia can be caused by diuretics, especially thiazide diuretics,[14] gastrointestinal sodium loss due to severe diarrhea, severe vomiting, and loss of sodium via skin due to excessive sweating.[15,16] Adrenal insufficiency, renal salt wasting and cerebral salt wasting are other causes of hypovolemic hyponatremia.[17,18] Some of the causes of Hypovolemic hyponatremia are heart failure, cirrhosis of liver and nephrotic syndrome.[19,20,21] Symptom of inappropriate antidiuretic hormone (SIADH) secretion, beer drinker's potomania, primary polydipsia and hypothyroidism are conditions which determined as cause of normotonic hyponatremia.[22,23]

Statement of the Problem

Acute and symptomatic hyponatremia management should attain resolution of symptoms, getting the normal serum sodium level with its predictive range and the absence of any overcorrection complications like osmotic demyelination syndrome.

Treating acute and symptomatic hyponatremia for clinicians who are working in resource limited setup where there is no available standard 3% sodium chloride solution is strenuous. Whether giving the locally made enteral table salt solution for this situation can outweigh the risk is not known yet.

There is some research in other countries (Kenya) that have considered giving an enteral table salt solution for symptomatic hyponatremia in ICU setting, but it lacks clarity in how much to give for each individual and time prediction in correcting the situation.

Even if there is a common practice in the emergency department of TASH and ZMH of preparing a locally made 3 % NaCl solution using enteral table salt and giving a calculated dose for patients hourly, it has not been supported by evidence yet. Due to this we do not know its effectiveness, efficacy and safety.

Retrospective evaluation of this practice and supporting it with evidence is the major aim of this research.

Justification of the study

Working in conditions where it is common to get Acute and symptomatic hyponatremia patient but lacking evidence as to whether the treatment we provide for them is benefiting them or not is arduous.

Retrospective evaluation of this common practice and identifying the effect, safety and gap of it with tangible evidence is the significance of this study. Knowing the practice's success along

with the absence of harm will help us in recommending the management to other resource limited setings.

Literature review

The management and outcome of severe and/or acute hyponatremia depends on the initial severity of symptoms. The celerity, duration and severity of the hyponatremia are important factors which play a major role in patient symptoms. Definition of acute are those who present within 48 hours while we will consider chronic presentation beyond 48 hours. [24]

The acute presentation can have mild, moderate or severe symptoms. In the ED, nausea with vomiting, confusion and headache were defined as moderately severe symptoms.
Cardiorespiratory distress, intractable vomiting, deep somnolence coma and seizure are determined as severe symptoms.[2] In one of prospective, single-center study where 3784 patients present in ED, about 166 (4.4%) have hyponatremia and approximately one-third of the patients were determined to have symptoms.[3]

Chronic presentation of hyponatremia usually manifest with weakness, vertigo, nausea and history of falls.[25] A prospective study which analyzed 5208 people aged 55 years or older (mean age, 70.3 years) to determine serum sodium levels at baseline, they detected 399 patients with mild hyponatremia (mean serum sodium level, 133.4 mEq/L) and There was higher rate of prior falls at baseline in hyponatremic patients when compared with people with a normal serum sodium level (23.8% vs 16.4%, respectively; $P < .01$). there was also higher rate of incident non vertebral fractures noted over 7.4 years of mean follow-up in patients with hyponatremia than in people without hyponatremia (23.3%vs 17.3%, respectively; $P < .004$) [26]

In elderly patients with chronic hyponatremia falls are a common ED presentation. There are studies which suggest hyponatremia will cause osteoporosis which can cause fractures and fall down injuries. A low sodium level has an effect on bone resorption and also inhibits osteogenesis. Due to this reason Hyponatremia is a secondary cause of osteoporosis and bone fractures. The risk of this condition will increase with the severity of hyponatremia. [25,27,28]

Severe but Chronic hyponatremia can have symptoms. In a prospective study, they engaged 298 patients with serum sodium level less than 125 mEq/L. From them 96% were chronic hyponatremia. The symptoms that they identified were nausea (44%), vomiting (30%), confusion (30%), headache (27%), and seizures (5%). seizures occur more for patients with serum sodium levels less than 110 meq/l. [29]

In ED serum glucose level should be determined when we get a hyponatremia patient in order to rule out hyperosmolar hyponatremia [30]. If available an ion-selective electrode should be used when sodium is determined in order to avoid the occurrence of pseudo hyponatremia, which occurs when there is a high lipid and protein levels.[31] Other important laboratory

investigations will be serum osmolality, creatinine, urea, Thyroid stimulating Hormone, serum cortisol level and urine analysis.[32]

The management of severe and/or acute hyponatremia is challenging. The European clinical practice guideline suggests the immediate infusion of 150 ml of 3 % sodium chloride (NaCl) solution over 20 minutes for moderately severe symptoms or severe symptoms. It also recommends repeating another dose if it doesn't increase the serum sodium level by 5 mmol/l. [2]

For mild to moderate symptoms the American guideline suggest a 2 ml/kg administration of 3% NaCl, with preferable rapid intermittent bolus. [33]

Generally the serum sodium level should be checked after 6-12 hours after initial treatment and symptomatic relief. And the determination should be continued on a daily basis. In acute symptomatic conditions the daily maximum serum sodium correction should be 8-10 mmol/l. [2]

For chronic hyponatremia and asymptomatic patients the management should rely on the volume status of the patient. If the patient is hypovolemic hyponatremia it's recommended to start isotonic crystalloids with 20ml/kg/24 hours. [34,35] For hypervolemic hyponatremia fluid restriction can suffice.[2] If the clinical condition of the patient allows us, it's better to withhold the diuretics, especially thiazide diuretics and other drugs that can induce hyponatremia. [32]

The concept of using an oral hypertonic saline for treatment of hyponatremia comes from marathon runners.in 2011 there was Prospective randomization trial which was done in Western States (161 km) Endurance Run, California. 47 finishers were screened and found to have exercised associated hyponatremia at the race end. 8 of them were randomized into the intervention protocol. The serum sodium in only the intravenous (IV) group changed significantly (from 130.8 to 134.6 mmol/L) over the 60 minutes post administration. But there was no similar effect demonstrated for the same dose orally. [36]

Another paper in 2020, which was done in Annual long-distance triathlon (3.8-km swim, 180-km bike, and 42-km run) at Mont-Tremblant, Quebec, Canada successfully randomized 20 participants to receive either an oral (n = 11) or IV (n = 9) bolus of hypertonic saline HTS). After treatment with IV, the mean discharge time was 75.8 minutes (SD 29.7) and for the oral treatment group 50.3 minutes with (SD 26.8) was the discharge time. Serum sodium before and after treatment were not significantly different in both groups. [37]

A case report which was published in 2014 on Hourly oral sodium chloride for the rapid and predictable treatment of hyponatremia provided another support to the idea of giving oral saline for treatment of hyponatremia. A 35-year-old female patient who had an optic chiasm glioma and ventriculo-peritoneal shunt for hydrocephalus developed acute hyponatremia (sodium 122 mmol/L). She was treated with calculated dose oral NaCl tablets hourly. Predictable and

successful increase in serum sodium concentration was achieved without clinical significant complications. [38]

Another prospective observational study was done at Kenyatta National Hospital Main Critical Care Unit on hyponatremic patients. Table salt had been prescribed. The study involves 40 consenting adult patients who fit the inclusion criteria during the course of their treatment. From them, 32 patients (80%) had normal sodium levels after 1 or 2 days of table salt administration. 4 patients (10%) had hypernatremia and 4 patients (10%) persisted with hyponatremia despite 2 days of table salt administration. [39]

In resource limited situations where there is no available 3 % NaCl solution, it has been a challenge in treating hyponatremia. The absence of any standard guideline and evidence in using the enteral table salt for hyponatremia management doubles the trouble at ED and even in other critical care settings like intensive care unit (ICU).

To our knowledge there is limited data in our country which show evidence on using enteral table salt for hyponatremia management. The 2021 Ethiopian standard treatment guideline (STG) suggests preparing the locally made 3% saline solution using a 2 and half teaspoon enteral table salt and 500 ml of tap water. The approximate rationale being, there are about 6 gm salts in 1 teaspoon which will have about 2400 mg of sodium. This makes about 104 mmol sodium in 1 teaspoon (tsp) of enteral table salt. When we add 2 and half tsp on 500ml of water, we will get about 256.5mmol of sodium. Calculating the dose for each individual requires consideration of the age, weight and sex and giving hourly is needed. [40] But this guideline should be supported with research based evidence.

The most feared complication of hyponatremia treatment is osmotic demyelination syndrome. Its common symptom is altered mental status followed by upper motor neuron pattern weakness.
There was a retrospective Observational Cohort Study, where they identified 45 cases of ODS (mean age 48.4 years, range 0.07 -- 75 years; 58% female patients). Common comorbidities included liver disease (27%, n = 12), alcoholism (44%, n = 20), and kidney failure (20%, n = 9). From them, Twenty-nine percent of patients had a rapid correction of hyponatremia. [41]

Conceptual Framework

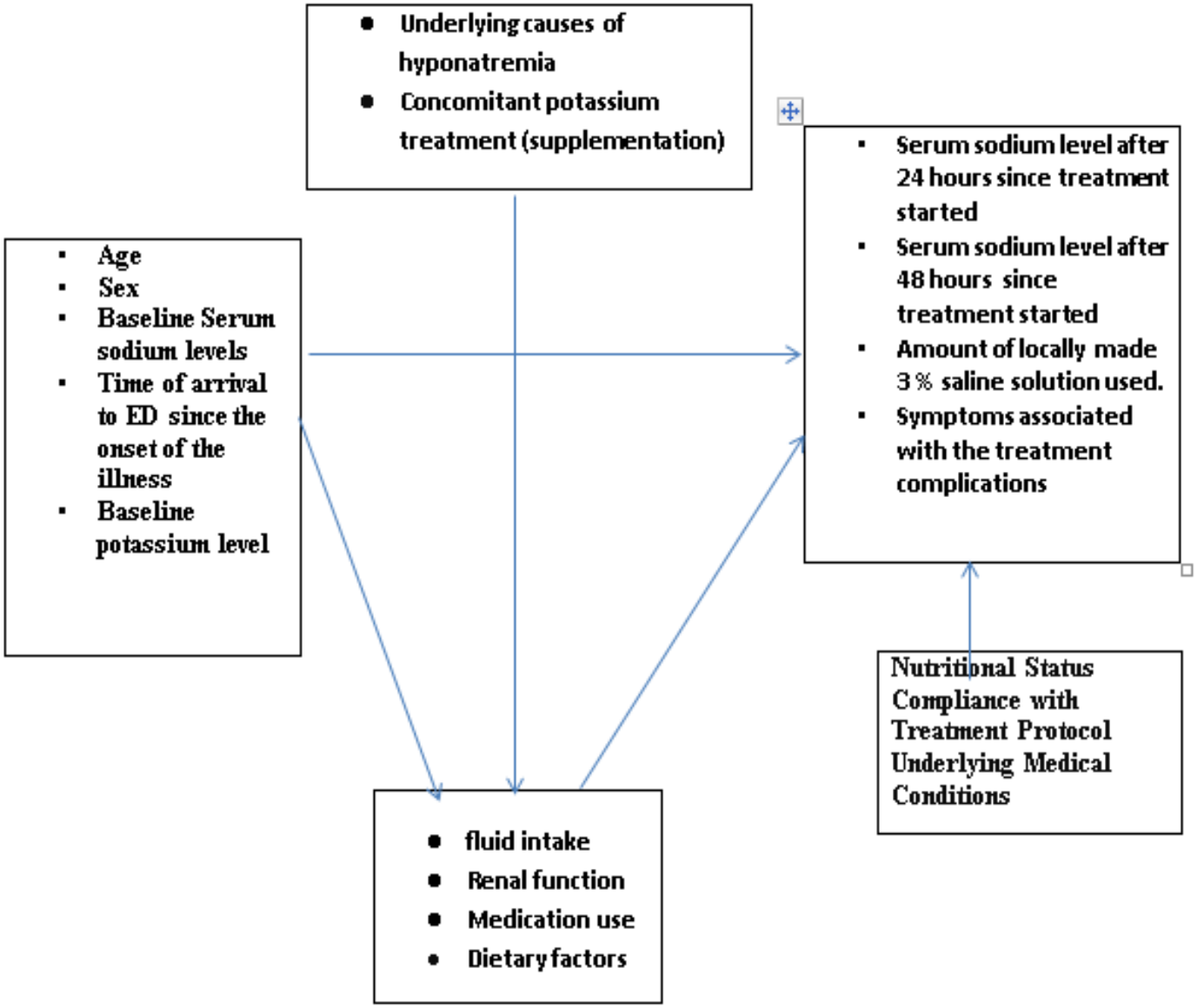


Figure 1: conceptual framework of Hyponatremia management using locally made enteral table salt solution.

The theoretical framework, assumptions and Tikur Anbessa specialized hospital (TASH) ED practice

Theoretical perspective of this study is trying to prepare the enteral table salt solution as a 3 % solution. After a locally made 3 % solution is prepared it will be calculated for each individual based on the Edelman equation and will be given hourly to potentiate the GI absorption.

Step 1: Solution preparation

According to the Ethiopian Standard treatment guideline (STG), 1 teaspoon of enteral table salt has 104 mmol sodium chloride (Nacl). [15] When 2 and half teaspoon is mixed with 500ml of water, there will be 260 mmol of Nacl in 500ml solution, which makes 520 mmol of Nacl in 1000 ml, which is approximate to the standard 3 % solution which has 513.5 mmol in 1000 ml solution.

Step 2: Calculation of the solution

1) Finding the change in sodium level.
   We used the simplified calculation formula of Edelman equation [42]
   Δ [Na+] =Na infuscate – Na current/TBW+1

   Where Δ [Na+] = change in sodium level
   Na infuscate = amount of sodium that the infuscate will have
   Na current= the patient current serum sodium level

2) Determine the rate of correction (mmol/day)

3) Calculate the amount of solution that will be given per hour
   Solution per hour= 1000ml *rate of correction/ Δ [Na+]

Step 3 : Giving the calculated dose hourly

Assumption of the theoretical framework

Each individual has a normal absorptive capacity.

Research objective

To determine the effectiveness of using a hourly based calculated dose of 3 % locally made table salt solution in the treatment of acute or/and symptomatic hyponatremia at the emergency department of a resource limited settings.

Specific objectives

- To demonstrate the prevalence and medical profiles of severe hyponatremia patients in the emergency department of resource limited settings.
- To assess the efficacy of oral 3% enteral table salt for the management of severe hyponatremia in patients presenting to emergency department of resource limited settings.
- To identify the incidence of treatment associated side effects from the use of locally made enteral table salt for the management of severe hyponatremia in emergency departments of resource limited settings.
- To identify factors associated with poor outcomes in the use of oral 3% enteral table salt for the management of severe hyponatremia in patients presenting to emergency department of resource limited settings.

Methodology

Study Area

The study conducted in Tikur Anbessa Specialized hospital (TASH) which is located in Addis Ababa city, the capital city of Ethiopia, located in the central part of Ethiopia at 9° 1′ 48″ north and 38° 44′ 24″ east a total population of 5,227,794, with geographical coverage of 540 km2(31). TASH is located in the Lideta sub-city and has a total of 600 physicians.

Study Period

A retrospective 1 year Data from July 1 2023 G.c. to June 30 2024 G.c was collected and analyzed.

Study Design

The study was a cross sectional retrospective study

Population

Target Population

The outcomes of the study aim are to be extrapolated to infer about all patients with Acute and/or symptomatic hyponatremia in low resource settings who would need to be treated with an hourly calculated dose of locally made oral 3% saline solution.

Source population

The study population will be sourced from patients who came from July 1 2023g.c to June-30 2024g.c in the emergency department of TASH.

Study population

All patients who came to the Emergency Department of TASH and who have acute and/or symptomatic hyponatremia and have been treated with a calculated dose of locally made 3 % saline in the study period.

Inclusion criteria

- All confirmed acute and/or symptomatic hyponatremia which have been treated with the locally made 3% enteral table salt solution in the determined months.

- The solution should be prepared per STG guideline (2 and ½ tea spoon and 500ml of water.)
- The calculated dose should be given hourly based.

Exclusion criteria

- Age <13
- Those who didn't have the repeated serum sodium level at least within 48 hours.
- Hyponatremia which is caused by hypervolemia (dilutional hyponatremia)

Sampling frame/Unit

Sample size

- The sample size is determined by using the formula for single population proportion estimation formula.
- Patients who are kept in emergency department is estimated to be 1000, considering (1)ED prevalence of hyponatremia to be 3% [3-6], makes 30 patients per month. If 1/3 of patients have been involved in the usual trend of hyponatremia management, it makes 10 patients per month. This makes 120 patients per 12 months.
- The sample was calculated by assuming a Confidence interval of 95%, 5% margin of error.

$$n = \frac{NZ\ x\ (p)\ (1-p)}{d\ (N-1)+Z\ p(1-p)}$$

- n = sample size with finite population correction
- N= size of target population = 120
- Z - z-score -1.96 (1)
- d - margin of error- 0.05
- p – estimated proportion of patients with Normally corrected range at day-1 post management, since there is no previous study, we took= 50%
- n - Sample size- 114
- Non-response rate is taken as 10% 114*(1/1-NR)= 127
- The sample size calculated for the secondary outcomes were similar with that of the primary outcome. (due to absence previous study on this perspective)

Study Instruments

A questionnaire was instituted to collect patients data from their chart and their first follow up after discharge from the hospital through Electronic medical record (EMR).

Sampling procedures

The study selected patients with simple random sampling from patients who have been kept at the emergency department of TASH who have Acute and/or symptomatic hyponatremia and who have been treated with a hourly based calculated dose of locally made 3 % enteral saline solution.

Data Collection Procedures

For this research, 2 data collectors and 1 supervisor, who are physicians and experts in the subject matter, were appointed. The data collection was executed using a pre-tested structured questionnaire, developed by reviewing various relevant literatures aligned with the study objectives. The questionnaire comprised closed-ended questions addressing socio-demographic characteristics, initial and serial electrolyte findings, and factors potentially influencing the results. The collected data was meticulously organized and analyzed by the principal investigator, ensuring that participants' identities remained confidential and were not disclosed to any third party.

Data collection steps

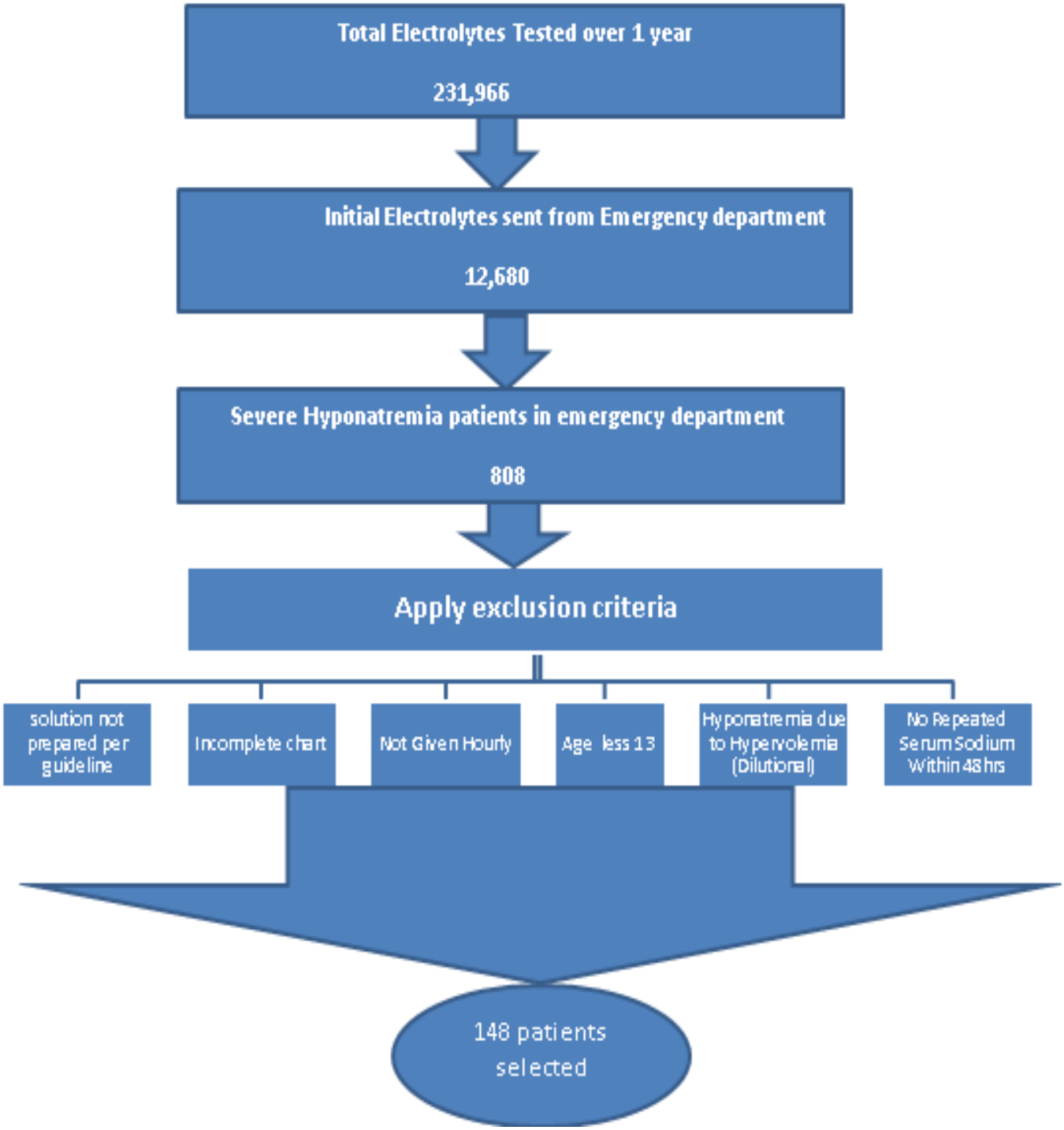


Figure 2: Data collection steps for the research.

Quality Control

To ensure the credibility and reliability of data in the study on "Prevalence, Management Outcome of Severe and/or Symptomatic Hyponatremia using Locally Made Enteral Table Salt Solution with its Associated Factors in Resource-Limited Setup," multiple quality control measures were implemented throughout the process. A pre-test on 10 patients not part of the main study was conducted to evaluate the research tool's clarity, relevance, and comprehensibility, leading to necessary adjustments. Two data collectors were trained thoroughly on the study objectives, research tool, and data collection techniques, with an emphasis on maintaining confidentiality and adhering to ethical guidelines. During data collection, regular supervision ensured adherence to protocols, addressing challenges, and maintaining data quality. The research team reviewed the data for completeness, consistency, and clarity, providing feedback as necessary. These measures minimized biases, errors, and discrepancies, thereby enhancing the study's credibility and reliability.

Quality control regarding the Laboratory Test

TASH uses advanced laboratory machines for analyzing electrolytes and renal function tests. It uses a Siemens dimension brand which has an ion-selective electrode (ISE) method with auto-analyzers. It's one of the best laboratories in the country that's accredited by Ethiopian food and medicine control authority (EFMCA).

Data Analysis

Data Collection and tallying were made and put for subsequent analysis into the statistics software SPSS version 26. First descriptive data analysis was done. We apply a normality test to understand the study type. Our data were abnormally distributed. So for the inferential statistics part we apply a non-parametric study.

We utilized the Related-Samples Friedman's Two-Way Analysis of Variance by Ranks to evaluate the effectiveness of the enteral table salt solution. The further inferential data analysis part involved using the Independent-Samples Kruskal-Wallis Test to examine the impact of hypokalemia on different patient factors. We also employed the Independent-Samples Mann-Whitney U Test to analyze the effect of Day 1 and Day 2 serum sodium levels on different ODS symptoms .we also performed factor analysis through regression to examine the influence of initial serum potassium levels, Day 1, day 2 serum sodium level and different ODS features. We also analyzed survival rates using the Kaplan-Meier curve to evaluate the association between serum sodium correction and patient mortality.

Operational definition

- Locally made 3 % saline = a solution which is prepared by using 2 and ½ of enteral table salt and 500 ml of tap water.
- Safe = correcting the hyponatremia with 8-10 meq/day and with no clinical features of overcorrecting related complications.
- Effectiveness = the percentage of patients with expected rise in serum sodium level within 24 and 48 hours duration.
- Hyponatremia: Sodium level below 135 mmol/L
- Hypernatremia: Sodium level above 155 mmol/L
- Acute onset = hyponatremia that occurs within 48 hours duration
- Symptomatic = acute or chronic hyponatremia with significant neurologic symptoms.
- Normally corrected (per-anticipated)= correction of hyponatremia by 4-12 meq/day for acute hyponatremia and 4-8 meq/day for chronic hyponatremia.
- Overcorrected= correction of hyponatremia by > 12 meq/day for acute hyponatremia and > 8 meq/day for chronic hyponatremia.
- Undercorrected= correction of hyponatremia < 4 meq/day for both acute and chronic hyponatremia.

Data Management

Data entry was done using EPI info. After data entry, cleaning was handled by the principal investigator.

Study Variables

Independent variables

- Age
- Sex
- Baseline Serum sodium levels
- Time of arrival to ED since the onset of the illness
- Underlying Primary diagnosis
- Comorbidities of the patient
- Amount of locally made 3 % saline solution used.
- Baseline potassium level

Dependent variables

- Serum sodium level after 24 hours since treatment started
- Serum sodium level after 48 hours since treatment started
- Symptoms associated with the treatment complications.
- Effectiveness in correction of hyponatremia

Ethical Consideration

The study was conducted after ethical clearance was obtained from the ethical Institutional Review Board (IRB) of the Addis Ababa University. Then, data was collected after getting an official letter of permission from the IRB office of the respective hospital. Patient's confidentiality was kept strictly. The analysis and subsequent dissemination of the research findings will be made in accordance with the ethical code and guidance of the ethical review committee Confidentiality was assured for the information provided by using an individual coding system, and questionnaires did not have any personal identifiers.

Result

There were 13,920 patients who came and were evaluated at ED of TASH from July 1 2023 G.c. to June 30 2024 G.c. An initial serum electrolyte was sent and collected for 12,680. Which makes for 91.1 % of patients which came in ED serum electrolyte was sent, among them 808 had severe hyponatremia which makes 5.8 % of total ED patients.

The total patients that were involved for subsequent study were 148. Among them 45.9 % were females and 54.1 % were male. The patient's age ranged b/n 15 to 87 with a median of 45 (IQR= 28).

Constituent 1: Initial diagnosis and comorbidities of patients

Half of patients were diagnosed to have sepsis on the initial evaluation of patients. And cancer and diabetes (DM) were the commonest comorbidity associated with the patients. Cancer accounts for 23 % of total patients while DM took 20.3 % (Table 1).

Table 1: initial diagnosis and comorbidity of patients

Comorbidities	**Frequency**	**Percent**
Cancer (oncology patients)	34	23%
Diabetes mellitus (DM)	30	20.3%
Hypertension	13	8.8 %
HIV	10	6.8%
Chronic liver Disease (CLD)	2	1.4 %
Systemic Lupus Erythematous (SLE)	2	1.4 %
Bronchial Asthma	1	0.7 %
Hypothyroidism	1	0.7 %
Old stroke	1	0.7 %
None of any comorbidities	53	35.8 %
Principal Diagnosis	**Frequency**	**Percent**
Sepsis	74	50 %
Meningitis	16	10..8 %
Tuberculosis (TB)	10	6.8 %
Stroke	9	6.1 %
Acute Gastroenteritis (AGE)	8	5.4 %
Multiple Electrolyte Abnormalities	8	5.4 %
Severe Dyspepsia	5	3.4 %
Bowel Obstruction	3	2 %
Shock	3	2 %
Intracranial hemorrhage (ICH)	3	2 %
Brain Abscess	1	0.7 %
Coma sec to?	1	0.7 %
Invasive Aspergillosis	1	0.7 %
Visceral Leishmaniasis (VL)	1	0.7 %
Infective Endocarditis (IE)	1	0.7 %
Peripheral Arterial Disease (PAD)	1	0.7 %
pneumocystis carinii pneumonia (PCP)	1	0.7 %
Subarachnoid Hemorrhage	1	0.7 %
Dengue Hemorrhagic Fever	1	0.7 %

Constitute 2: Hyponatremia symptoms during ED presentation

Among total patients 32.4 % had either mild hyponatremia symptoms, 25.7 % severe symptoms and 33.8 % patients had chronic symptoms. From acute symptoms Nausea and vomiting took the leading percentage (16.2 %) while generalized weakness is the most common one from chronic symptoms. (Table 2)

Table 2: symptoms of severe hyponatremia

Acute Symptoms	**Frequency**	**Percent**
Nausea and Vomiting	36	16.2 %
Confusion	27	12.2 %
Coma	25	11.3 %
Headache	23	10.4 %
Seizures	14	6.3 %
Drowsiness	4	1.8 %
None of Acute Symptoms	93	41.9 %
Chronic symptoms	**Frequency**	**Percent**
Weakness	47	26.7 %
History of Falls	19	10.8 %
Vertigo	12	6.8 %
None of chronic symptoms	98	55.7 %

Constitute 3: Initial and subsequent laboratory results

Based on the initial laboratory results, the median serum sodium level among patients was 118 mmol/L (IQR= of 10 mmol/L), this shows that there is a minimal variation. In contrast, the initial urea levels had a median of 35 mg/dL (IQR of 25 mg/dL) reflecting greater variability in kidney function at baseline

On Day 1, the median serum sodium level was 127 mmol/L (IQR= of 14 mmol/L), showing a notable increase from the baseline serum level.

By Day 2, the median level further rose to 132 mmol/L with an IQR of 13 mmol/L, indicating a gross increment of serum sodium level after the initiation of the management.

From the total patients, 39 (26.4 %) had hypokalemia, 107 (72.3 %) had normal potassium levels and only 2 (1.4 %) hyperkalemia range.

Table 3: Serum sodium level at different time distribution

Serum sodium	**Median**	**Interquartile range (IQR)**	**Range**
Initial serum sodium	118	10	35
Day-1 serum sodium	128	8	64
Day 2 serum sodium	132	8	65

Constitute 4: the Local table salt and its effectiveness

The day 1 total amount of 3% locally made enteral table salt solution intake shows a median of 720 ml (IQR of 110ml) and on day 2 median amount was 600ml (IQR=380 ml). When we evaluate the Day 1 and Day 2 serum sodium levels after they took the 3 % enteral table salt solution 13 patients (8.8 %) were under-corrected, 99 patients (66.9 %) achieved normal correction as anticipated and 36 patients (24.3 %) were overcorrected.

Table 4: Total enteral table salt solution used

Total amount (ml/24hours)	**Median (ml/24hr)**	**IQR (ml/24hr)**	**Range**
Total amount used on day-1	720	240	600
Total amount used in day 2	600	285	840

Constitute 5: frequency of Osmotic Demyelination Syndrome (ODS) symptoms after treatment initiation

Following the initiation of management, some patients developed ODS symptoms. The most common symptoms observed after treatment initiated were vomiting, that was reported in 7.6% of patients, and diarrhea, seen in 6.4% of patients. The other symptoms noticed were seizure, abnormal posturing and nystagmus.

Table 5: ODS symptoms after treatment

ODS symptom	Frequency	Percent
Vomiting	13	7.6%
Diarrhea	11	6.4%
Worsening from baseline consciousness level	8	4.7 %
Seizure	3	1.8 %
Abnormal posturing (movement disorder)	6	3.5 %
Nystagmus	1	0.6 %
No any symptoms	129	75.4 %

Constitute 6: Effectiveness of giving 3 % enteral table salt solution hourly in severe and/or acute hyponatremia management

The locally made enteral table salt solution effectively alters serum sodium levels from the initial measurement to Day 1 and Day 2 measurement. Since we have a three serial serum sodium level (initial, day-1 and day-2), it was tested by Related-Samples Friedman's Two-Way Analysis of Variance by Ranks. This shows a highly statically significant p-value (0.000). This indicates that using a 3 % enteral table salt solution hourly is effective in reaching the targeted serum sodium level after 24-48 hours.

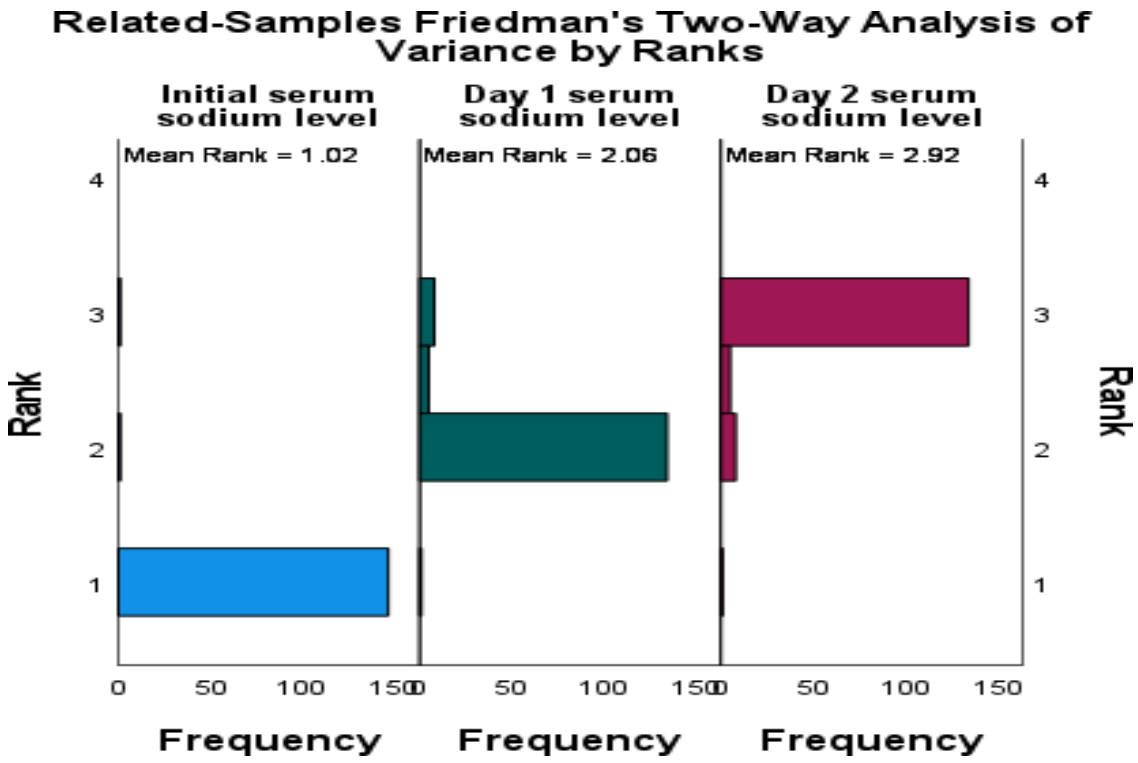
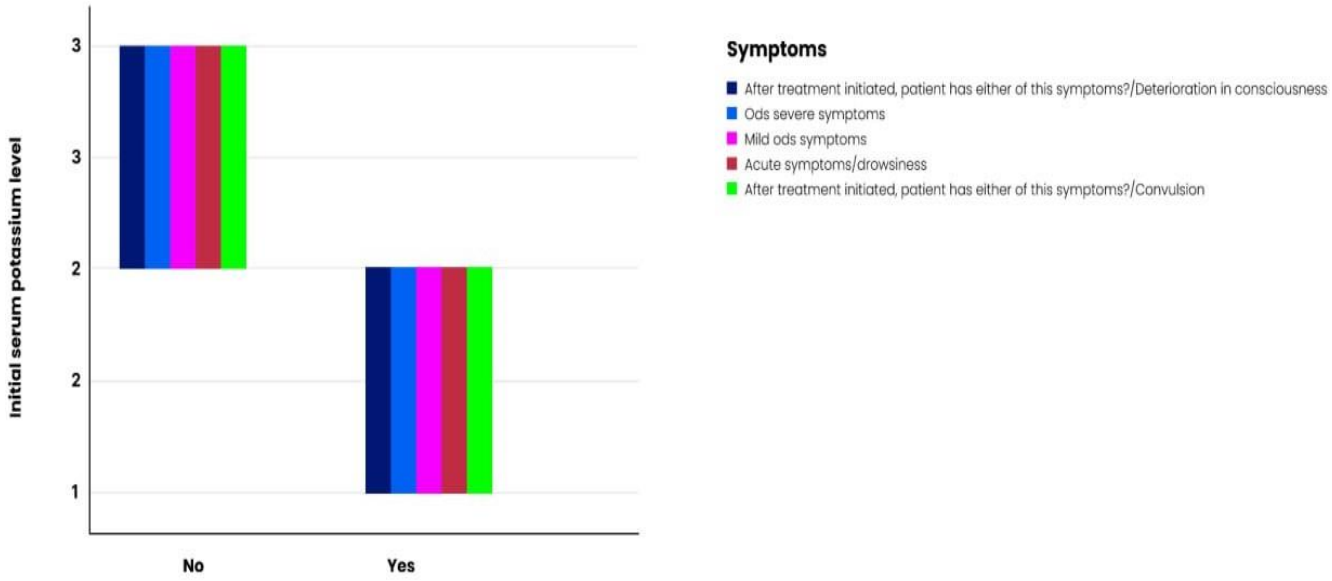


Figure 3: Friedman's two way analysis of variance by rank

Constitute 6: EFFECT of serum potassium level on Management of hyponatremic patients

There is a significant association between the initial serum potassium level and the overall outcome of severe and/or acute hyponatremia management in our study. Using the Independent-Samples Kruskal-Wallis Test, we found that hypokalemia notably impacts Day 1 serum sodium levels, showing greater variability ($p < .001$). And it also has a significant effect on Day 2 serum sodium level ($P<0.005$). There was a statistically very significant association with the ODS symptoms too. Generally Patients with mild ODS symptoms are more likely to exhibit hypokalemia ($p <0 .001$) and also for severe ODS symptoms which it shows ($p<0.013$).



1=Hypokalemia

2= Normal serum potassium level

3= hyperkalemia

Figure 4: the combined graph of Independent-Samples Kruskal-Wallis Test between different ODS symptoms and serum potassium level.

Constitute 7: Factor Associated with Hyponatremia management

Factors that affect Day 1 and Day 2 serum sodium level and their impact on ODS symptoms

Day 1 and Day 2 serum sodium values can be significantly influenced by initial serum potassium levels (Day 1: B = -7.012, p < .001; Day 2: B = -6.432, p < .001). The presence of drowsiness among initial acute symptoms of hyponatremia was significantly associated with higher serum sodium levels on both Day 1 (B = 11.198, p = .002) and Day 2 (B = 8.240, p = 0.053).
Furthermore, among chronic symptoms of hyponatremia, a history of falls was significantly associated with higher Day 2 serum sodium levels (B = 5.192, p = 0.026).

There is a significant association between Day 1 and Day 2 serum sodium levels with various ODS symptoms in our result. Using the Independent-Samples Mann-Whitney U Test, we found that Day 1 serum sodium levels significantly impact mild ODS symptoms ($p = 0.008$) and are highly associated with convulsions ($p = 0.040$). Meanwhile, Day 2 serum sodium levels showed a significant effect on mild ODS symptoms ($p = 0.005$).

Factors associated with overcorrection

Overcorrection was highly associated with the patient's lower initial serum sodium level (aOR=0.912, CI=0.860,0.966) and hypokalemia(aOR=0.008 , CI=0.002,0.031). It's slightly associated with the total day-1 3 % solution amount (aOR=1.005 CI=1.001, 1.008).

Patients who had overcorrection were more prone to develop mild and severe ODS symptoms.

Table 6: factors associated with overcorrection

Factors	**p-value**	**Adjusted Odds ratio**	**CI**
initial serum sodium level	p < .001	0.912	0.860, 0.966
potassium level	p < 0.001	0.008	0.002 & 0.031
total day 1 3 % solution Amount	p < .001	1.005	1.001, 1.008
day 1 serum sodium level	p < .001	1.185	1.098, 1.280
day 2 serum sodium level	p < .001	1.109	1.048, 1.173
mild ODS symptoms	p < .001	16.022	6.194, 41.443
severe ODS symptoms	p < .001	8.770	2.134, 36.035

Factors those are associated with under correction

From our study the most statically significant factor that we get for under correction was the total amount of 3 % solution that was taken on day-1 (aOR=0.995, CI=0.0991, 0.998). Patients who had undercorrection were more associated with Death (aOR=9.825, CI=1.927, 50.106). But this wide range of the CI can tell us indirectly that this association may be caused by a chance or indicates the small sample size.

Table 7: factors associated with undercorrection.

Clinical condition	Adjusted Odds ratio	p-value	95 % CI
total amount 3 % solution intake on day-1	0.995	p < .001	0.991, 0.998
day 1 serum sodium level	0.819	p < .001	0.743 , 0.903
day 2 serum sodium level	0.839	p < .001	0.767, 0.917
Death	9.825	p < .001	1.927 - 50.106

Factors associated with ODS Symptoms

Mild ODS symptoms was associated with hypokalemia (P-value >0.001, aOR=6.929,CI=2.904,16.530), initial serum sodium level (P-value= 0.016, aOR=0.933, CI=0.8810,0.987) and overcorrection(p < .001, aOR=16.022 CI=6.194, 41.443). severe ODS symptoms were associated with hypokalemia (P-value=0.021 aOR=4.773 CI=1.27 , 17.942) and overcorrection (P-value p < .001, aOR=8.770, CI=2.134, 36.035).

Association of Death with correction rate

Out of the total patients, 7 passed away, representing 4.7%. This mortality data is crucial for understanding the outcomes and effectiveness of the treatment administered. To determine whether the correction rate is associated with mortality, we used a Kaplan-Meier curve to illustrate the cumulative hazard of different correction rates over time. The cumulative hazard increases more sharply for the under-corrected group compared to the overcorrected and normally corrected groups. This indicates that under-correction was associated with a higher mortality rate than the overcorrection and normal correction groups.

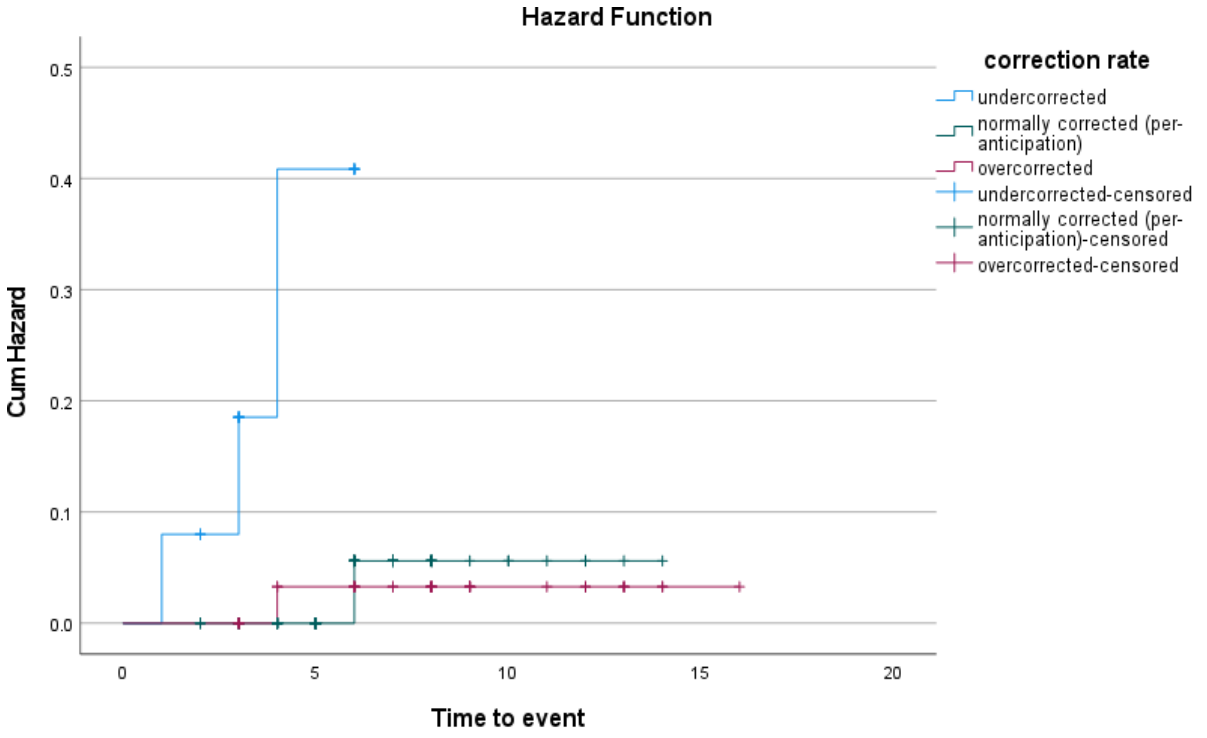


Figure 5: Kaplan Meier curve of Correction rate over death.

Discussion

Using an hourly based calculated dose of 3 % table salt enteral solution is effective in managing the acute and/or symptomatic hyponatremia in resource limited setup. When we evaluate the Day 1 and Day 2 serum sodium level, 13 patients (8.8 %) were under-corrected, 99 patients (66.9 %) achieved normal correction as anticipated and 36 patients (24.3 %) were overcorrected. When this was tested by Related-Samples Friedman's Two-Way Analysis of Variance by Ranks, it shows a highly statically significant p-value (0.000).

In this study, the anticipated bias was, selection bias considering the retrospective cross sectional nature of the study, we clearly defined the target population and random sampling methods were used to define the sampling frame. Information bias was another anticipated challenge. To reduce this bias, we utilized a standardized and validated data collection tool. Additionally, we employed the triangulation method, using multiple data sources such as patient charts, electronic medical records (EMR), and laboratory results to ensure comprehensive and accurate data collection.

There is not much data regarding the prevalence of severe hyponatremia in emergency departments of resource limited areas. From western's data the prevalence of severe hyponatremia in the emergency department was about 0.3%-0.92[43-44]. This is significantly lower than our study which is 5.8%. The possible reason for such a profound difference might be because most of our patients are critically ill, with/out comorbidities which might have been on different diuretic medications. But to know the exact reason another research study should be done focusing on causes of severe/profound hyponatremia in resource limited setup.

The median age of hyponatremic patients in our study was 45(IQR= 28). This is significantly lower than the previous study, which shows higher prevalence of severe hyponatremia in older age groups (1.9% vs. 0.3%, $p < 0.001$). (44)

In previous studies there was a significant association between the prevalence of hyponatremia in sepsis patients which is 69.47% (n=95), but there was no evidence of association with severe hyponatremia [45]. In our study 50 % of patients were associated with sepsis but there was no statistically significant evidence of association with the outcome of septic patients. The other patients 10.8 % had meningitis and 6.8 % was diagnosed to have Active Tuberculosis (TB)

Among comorbidities which are associated with severe hyponatremia that have been determined from previous research were 67 % was hypertension, 15 % had congestive heart failure, 21 % had chronic renal failure 28 % were determined to have pulmonary disease.[46] In our study oncologic patients were the most common one which took 23 %. Followed by diabetes mellitus

(20.3%), hypertension 8.8% that is significantly different from the previous studies. The major reason for this significant difference might be TASH is the only referral center for most oncology patients and it's one of the few oncology centers in the country, which makes most patients visit the ED of this hospital. . And it's common to refer such patients to the emergency department from the oncologic clinic and ward whenever they have complications.

There are various studies regarding the symptoms of hyponatremia for patients with moderate-severe level Na(120-130 mmoles/L) who usually present with nausea, emesis and abdominal cramps [47, 48]

With profound acute hyponatremia (below 115 mmoles/liter) central nervous system (CNS) manifestations will predominant with the commonest one being weakness, lethargy, restlessness, confusion, delirium and impaired mentation [49] the other severe acute manifestations can be abnormal body movement such as muscular twitching and seizure [50, 51, 52, 53, 54]

For chronic hyponatremia the top neurological presentation has been focal weakness, hemiparesis, ataxia and Babinski sign [47, 49, 52]. Patients with chronic symptoms have also been presented with generalized weakness and falling injury. The comparison study regarding history of falling when it compared with people normal serum sodium levels were significantly high (23.8% vs 16.4%, respectively; $P < .01$) [55]. In our study 32.4 % had either of mild hyponatremia symptoms, 25.7 % severe symptoms and 33.8 % patients had chronic symptoms. Among the acute symptoms Nausea and Vomiting were the leading ones (16.2 %) followed by confusion (12.2 %) and coma (11.3 %). This is comparable with the previous studies. Among chronic manifestations, generalized weakness (26.7%) and patients with a history of falls (10.8 %) were the commonest symptoms.

There is significant evidence that supports the effectiveness of standard 3 % IV saline in treating severe and/or acute hyponatremia management. For example in one of the case series where they used a standard 3 % saline solution for treatment of severe hyponatremia, they include 71 episodes of hyponatremic encephalopathy in 64 patients.[56] Their mean initial sodium level was 114.1±0.8 (SEM) mEq/L. they were following their patients at 3, 12, 24, and 48 hours. The solution was able to increase their serum sodium level to 117.9±1.3, 121.2±1.2, 123.9±1.0, and 128.3±0.8 mEq/. When we try to compare from our result and if we take the initial serum sodium level, day 1 serum sodium level and day 2 serum sodium level it will be 114.1±0.8 (SEM), 123.9±1.0 and 128.3±0.8 mEq/ respectively[56]. This is comparable with our study where the median and IQR of the initial, day-1 and day-2 serum sodium levels are 118 (IQR=10), 128 (IQR=8) and 132(IQR=8) respectively. This can imply that using a locally made calculated dose enteral table salt solution has a comparable effect in treating severe and/acute hyponatremia in resource limited set up.

Another study that tries to see the effectiveness of enteral table salt for treatment of hyponatremia in ICU states that 80 % (32/40) patients had normal sodium levels within 2 days.

Where 10 % (4/40) patients had hypernatremia and another 10 % had hyponatremia. In their study the mean change in sodium level was 5.5 % and 6.8 % on day 1 and day 2 serum sodium level respectively. (39) In our study the main focus was whether our enteral local solution is effective in getting the desired correction rate. Normal correction was defined in our study for acute hyponatremia to be 8-10 mmol, and for chronic symptomatic hyponatremia it was 4-6 mmol. Overcorrection was defined as a correction rate higher than 10 mmol/day for acute one and if it exceeded 8 mmol/day for chronic one. Undercorrection was defined for both cases if the correction rate is less than 4 mmol/day. Based on that definition our result shows that 99 patients (66.9 %) achieved normal correction as anticipated and 36 patients (24.3 %) were overcorrected and 13 patients (8.8 %) were under-corrected. This was analyzed using a non-parametric test, Related-Samples Friedman's Two-Way Analysis of Variance by Ranks and it shows a highly significant p-value (0.000). This shows that the 3 % locally made enteral table salt solution is statically effective in altering the initial serum sodium level and can be used for treatment of severe and/acute hyponatremia management in resource limited settings.

One study shows the use of the predictive equation using a standard 3 % IV solution. They used a formula by Rose BD. It resulted in an appropriate correction for most patients. In one study where they used a predictive equation for calculating a 3 % standard solution, it demonstrated a good correction rate. It showed that 84.7% had a normal correction rate whereas 14.3% had under-correction and 1 % had overcorrection. Factors that were determined as risk factors for overcorrection were low BMI and low serum [K], and were also significantly associated with the appropriate correction of hyponatremia in this study. (57) in our study where we were applying a predictive equation using Edelman Equation and we had slightly lower under-correction rate than them (8.8 % vs 14.3%) where their overcorrection rate was significantly lower than our study. (1 % vs 24.3 %).

In another retrospective single-center cohort study that was done in patients admitted to the ICU with serum sodium < 120 mmol/L between 1 January 2017 and 8 March 2023. They involved 181 patients from electronic data and their overcorrection rate was 34% at 48 hours. The identified risk for the overcorrection was, initial severe symptoms (seizures/arrhythmias) and lower admission sodium concentration. (58) In our study, multivariate logistic regression model was used and it shows overcorrection is associated with initial potassium level (OR=0.008,CI (0.002, 0.031)), total amount of solution on day 1 (OR=1.005,CI (1.001, 1.008)) and initial serum sodium level (OR=0.912, CI=(0.860, 0.966)).

There was a significant association between the overcorrection rate and ODS symptoms in our study. Generally for mild ODS symptoms overcorrection (OR=16.022 CI=6.194, 41.443) and initial serum potassium level (Independent-Samples Kruskal-Wallis Test shows p value of P<0.005) were the most predictive factors. It was also slightly affected by day 2 total amount of 3% enteral table salt solution administered (p = 0.015, OR = 0.998). For severe ODS symptoms overcorrection (OR=8.770, CI=(2.134,36.035)) and initial potassium level (Independent-Samples Kruskal-Wallis Test shows p value of, p<0.013) were the predictors. There are a range of studies

regarding the correlation of ODS with rate of correction. One study in rats showed a stronger correlation of ODS with the rate of correction [59]. Others explain that the correlation is more with the magnitude of correction [60]. Whereas other claims that both rate and magnitude has effect on ODS development [61, 62, 63, 64] the other explanation was that overcorrection has more impact on chronic hyponatremia management than the acute one [65]. More recent studies explain that ODS to be rare and unrelated to overcorrection rate.[66] In our study the patients were treated with the solution once the treating team believed that it's acute or chronic severe hyponatremia. The major decision for the treatment was based on the level of severity of symptoms, profoundness of the initial serum sodium level and duration (acute). Since there were a good number of patients with chronic hyponatremia (33 %) which might have an impact on the association of overcorrection with ODS symptoms. The other risks include those with alcohol abuse, concomitant hypokalemia, malnutrition and liver disease [67]. There is no association between overcorrection and death in our study. This is similar to most other studies. In one of the studies where they analyzed a total of 412 patients, the rate of overcorrection was 27.9%. But overcorrection was not associated with in-hospital mortality [68]. This same study shows that 21.1% had under corrected, and under correction was associated with an increase in hospital length of stay. (9.3 days; 95% CI, 1.9-16.7 days)[68].

There is scarcity of previous studies on possible risk for under correction in severe hyponatremia management. In one of the study determined increase body weight (≥ 100 kg) as major factor for under-correction (OR 5.11, 95% CI 1.35–19.29).[69] on another study avoidance of hypertonic saline (aOR, 2.52; 95% CI: 1.12-5.66; p=0.029) and having neuropsychiatric disorder (aOR, 2.60; 95% CI: 1.10-6.11; p=0.025) were associated with under-correction.[70] In our study the day 1 total amount of the solution was the statically significant risk factor for undercorrection.(OR= 0.995 CI=(0.991, 0.998)).

In our study undercorrection was significantly associated with mortality (OR=9.825, CI= (1.927 - 50.106). Important to note that the CI is wide, that indicates uncertainty regarding the true value of the odds ratio. Possible reasons for it might be small sample size or a large amount of variability in the data. Overall there is a statistically significant association between death in the hospital and the undercorrection, but the magnitude of the effect is uncertain. The Kaplan Meier curve also increases more sharply for the under-corrected group compared to the overcorrected and normally corrected groups. This indicates that under-correction was associated with a higher mortality rate than the overcorrection and normal correction groups. This result has similarity with some of previous studies. In the previous study that we mentioned, there was a significant association between death and under-correction (aOR=6.68 CI= (2.00 -- 22.32))[70].

Limitation of the study

Considering the retrospective nature of the study there might be inconsistently documented data which might affect reliability of the study. There were different unmeasured confounding variables in the study (daily diet, nutritional status of the patient, BMI and other parameters) which might affect the result of the study. We had a small sample size which can affect the precision of the estimates. Since we didn't have a control group, it's difficult to determine the relative effects of each exposure that makes it difficult to draw a cause and effect relationship between variables.

Conclusion

The prevalence of severe hyponatremia in resource limited setup is higher than the western's data(5.8 % vs 0.92).Using 3 % locally made enteral table salt solution is effective in treatment of severe and/acute hyponatremia management in resource limited settings (Related-Samples Friedman's Two-Way Analysis of Variance by Ranks p-value (0.000)). Calculating the solution using Edelman Equation is essential and effective for the management by reducing the risk of overcorrection (normal correction rate=66.9 %). Overcorrection was associated with initial potassium level (OR=0.008,CI (0.002, 0.031)), total amount of solution on day 1 (OR=1.005,CI (1.001, 1.008)) and initial serum sodium level (OR=0.912, CI=(0.860, 0.966)). Using a day 1 lower amount of locally made solution was a significant risk factor for under-correction (OR= 0.995 CI=0.991, 0.998).

For both mild and severe ODS symptoms overcorrection and initial serum potassium level were statically significant predictor. There was no association b/n the ODS symptoms and rate of death. There was no correlation between the principal diagnosis and comorbidities of patients with the deaths. Undercorrection was the only statically significant component for the deaths in the study.

Recommendation

We can consider giving a calculated locally made 3 % enteral table salt for patients with severe and/or acute hyponatremia management in resource limited settings where there are challenges in obtaining standard 3 % hypertonic solution. But a further and higher level of study is warranted, possibly an RCT that will compare our enteral table salt solution with the standard 3 % hypertonic solution.

In resource-limited settings where standard 3% hypertonic solutions are unavailable, administering a calculated, locally made 3% enteral table salt solution could be a viable option for managing severe and/or acute hyponatremia. However, further investigation is warranted.

Reference

1. Barash P et al, editors: clinical anesthesia (6th ed), Philadelphia, 2009, Lippincott Williams & wilkins.
2. Clinical practice guideline on diagnosis and treatment of hyponatremia, Goce Spasovski, Raymond Vanholder, Bruno Allolio, Djillali Annane, Steve Ball, Daniel Bichet, Guy Decaux, Wiebke Fenske, Ewout J Hoorn, Carole Ichai, Michael Joannidis, Alain Soupart, Robert Zietse, Maria Haller, Sabine van der Veer, Wim Van Biesen, Evi Nagler, Nephrology, Dialysis, Transplantation 2014, 29 Suppl 2: i1-i39`
3. Burst V .Etiology and epidemiology of hyponatremia. Front Horm Res.2019;52:24-35.doi: 10.1159/000493234
4. Adrogué, Horacio J.*,†; Madias, Nicolaos E.‡,§. The Challenge of Hyponatremia. Journal of the American Society of Nephrology 23(7):p 1140-1148, July 2012.
5. Richard H. Sterns, Stephen M. Silver, J. Kevin Hix, Chapter 44 - Hyponatremia, Editor(s): Robert J. Alpern, Orson W. Moe, Michael Caplan, Seldin and Giebisch's The Kidney (Fifth Edition), Academic Press, 2013, Pages 1511-1539, ISBN 9780123814623,
6. Davila CD, Udelson JE. Hypervolemic hyponatremia in heart failure. Front Horm Res. 2019;52:113-129.doi:10.1159/000493242
7. Solà E ,Ginès P .Hypervolemic hyponatremia (liver).Front Horm Res.2019;52:104-112.doi:10. 1159/000493241
8. Verbalis JG. Hyponatremia and hypoosmolar disorders .In :GilbertS J, Weiner DE,eds. National KidneyFoundation'sPrimeronKidneyDiseases.7th ed.Elsevier;2018:68-76.
9. Journal of the American Society of Nephrology: JASN 2017, 28 (5): 1340-1349
10. Gennari FJ. Hypo-hypernatraemia: disorders of water balance. In: Davison AM, Cameron JS, Grünfeld J-P, Kerr DNS, Ritz E, Winearls CG, eds. Oxford textbook of clinical nephrology. 2nd ed. Vol. 1. Oxford, England: Oxford University Press, 1998:175-200.
11. McGee S, Abernethy III WB, Simel DL. Is this patient hypovolemic?. Jama. 1999 Mar 17;281(11):1022-9.
12. Pourmand A, Pyle M, Yamane D, Sumon K, Frasure SE. The utility of point-of-care ultrasound in the assessment of volume status in acute and critically ill patients. World journal of emergency medicine. 2019;10(4):232.
13. Long E, Oakley E, Duke T, Babl FE, Paediatric Research in Emergency Departments International Collaborative (PREDICT. Does respiratory variation in inferior vena cava diameter predict fluid responsiveness: a systematic review and meta-analysis. Shock. 2017 May 1;47(5):550-9.
14. Arampatzis S, Funk GC, Leichtle AB, Fiedler GM, Schwarz C, Zimmermann H, Exadaktylos AK, Lindner G. Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis. BMC medicine. 2013 Dec;11:1-6.

15. Hew-Butler T, Loi V, Pani A, Rosner MH. Exercise-associated hyponatremia: 2017 update. Frontiers in medicine. 2017 Mar 3;4:21.
16. Seal AD, Anastasiou CA, Skenderi KP, Echegaray M, Giannakouris N, Tsekouras YE, Matalas AL, Yannakoulia M, Pechlivani F, Kavouras SA. Incidence of hyponatremia during a continuous 246-km ultramarathon running race. Frontiers in Nutrition. 2019 Oct 11;6:458860.
17. Spital A. Hyponatremia in adrenal insufficiency: review of pathogenetic mechanisms. Southern medical journal. 1982 May 1;75(5):581-5.
18. Kobayashi A, Otsuka Y, Yoshizawa T, Tomita M, Asada H, Ikeda J, Saito M, Tojo K, Kuriyama S, Hosoya T. Severe hyponatremia caused by secondary adrenal insufficiency in a patient with giant pituitary prolactinoma. CEN case reports. 2013 Nov;2:184-9.
19. Dunlap ME, Hauptman PJ, Amin AN, Chase SL, Chiodo III JA, Chiong JR, Dasta JF. Current management of hyponatremia in acute heart failure: a report from the Hyponatremia Registry for Patients With Euvolemic and Hypervolemic Hyponatremia (HN Registry). Journal of the American Heart Association. 2017 Aug 3;6(8):e005261.
20. Alukal JJ, John S, Thuluvath PJ. Hyponatremia in cirrhosis: an update. Official journal of the American College of Gastroenterology| ACG. 2020 Nov 1;115(11):1775-85.
21. Palmer BF, Alpern RJ. Pathogenesis of edema formation in nephrotic syndrome. Kidney International Supplement. 1997 Jun 2(59).
22. Sanghvi SR, Kellerman PS, Nanovic L. Beer potomania: an unusual cause of hyponatremia at high risk of complications from rapid correction. American Journal of Kidney Diseases. 2007 Oct 1;50(4):673-80.
23. Sailer CO, Winzeler B, Christ-Crain M. Primary polydipsia in the medical and psychiatric patient: characteristics, complications and therapy. Swiss medical weekly. 2017 Nov 1;147(4344):w14514-.
24. Adrogué HJ, Tucker BM, Madias NE. Diagnosis and Management of Hyponatremia: A Review. JAMA. 2022 Jul 19;328(3):280-291.
25. Barsony J, Kleess L, Verbalis JG. Hyponatremia is linked to bone loss, osteoporosis, fragility and bone fractures. Front Horm Res. 2019;52:49-60
26. Hoorn EJ, Rivadeneira F, van Meurs JB, et al. Mild hyponatremia as a risk factor for fractures: the Rotterdam Study.J Bone Miner Res. 2011;26(8): 1822-1828
27. Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA. Hyponatremia independent of osteoporosis is associated with fracture occurrence. Clinical Journal of the American Society of Nephrology. 2010 Feb 1;5(2):275-80.
28. Corona G, Norello D, Parenti G, Sforza A, Maggi M, Peri A. Hyponatremia, falls and bone fractures: A systematic review and meta-analysis. Clinical endocrinology. 2018 Oct;89(4):505-13.
29. Nigro N, Winzeler B, Suter-Widmer I, et al. Symptoms and characteristics of individuals with profound hyponatremia: a prospective multicenter observational study.J Am Geriatr Soc. 2015;63(3): 470-475.
30. Verbalis JG, Goldsmith S , Greenberg A, etal. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am JMed.2013;126(10)(suppl1):S1-S42.doi:10.1016/j. amjmed.2013.07.006
31. Svenja Ravioli, Shawki Bahmad, Georg-Christian Funk, Christoph Schwarz, Aristomenis Exadaktylos, Gregor Lindner, Risk of Electrolyte Disorders, Syncope, and Falls in Patients Taking Thiazide Diuretics: Results of a Cross-Sectional Study, The American Journal of Medicine ,Volume 134, Issue 9, 2021, Pages 1148-1154,

32. Lindner G, Schwarz C, Haidinger M, Ravioli S. Hyponatremia in the emergency department. Am J Emerg Med. 2022 Oct;60:1-8. doi: 10.1016/j.ajem.2022.07.023. Epub 2022 Jul 19. PMID: 35870366.
33. Baek SH, Jo YH, Ahn S, Medina-Liabres K, Oh YK, Lee JB, Kim S. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: the SALSA randomized clinical trial. JAMA internal medicine. 2021 Jan 1;181(1):81-92.
34. Lindner G, Schwarz C. An update on the current management of hyponatremia. Minerva Medica. 2012 Aug 1;103(4):279-91.
35. Ruiz-Sánchez JG, Meneses D, Álvarez-Escolá C, Cuesta M, Calle-Pascual AL, Runkle I. The effect of the dose of isotonic saline on the correction of serum sodium in the treatment of hypovolemic hyponatremia. Journal of Clinical Medicine. 2020 Nov 5;9(11):3567.
36. Rogers IR, Hook G, Stuempfle KJ, Hoffman MD, Hew-Butler T. An intervention study of oral versus intravenous hypertonic saline administration in ultramarathon runners with exercise-associated hyponatremia: a preliminary randomized trial. Clin J Sport Med. 2011 May;21(3):200-3.
37. Bridges E, Altherwi T, Correa JA, Hew-Butler T. Oral Hypertonic Saline Is Effective in Reversing Acute Mild-to-Moderate Symptomatic Exercise-Associated Hyponatremia. Clin J Sport Med. 2020 Jan;30(1):8-13.
38. Kerns E, Patel S, Cohen DM. Hourly oral sodium chloride for the rapid and predictable treatment of hyponatremia. Clin Nephrol. 2014 Dec;82(6):397-401.
39. MOHAMMED YAHYA RASHID, THE EFFECTIVENESS OF ENTERAL TABLE SALT IN HYPONATREMIA AT THE KENYATTA NATIONAL HOSPITAL, CRITICAL CARE UNIT, UNIVERSITY OF NAIROBI, 2017
40. STANDARD TREATMENT GUIDELINE FOR GENERAL HOSPITALS IN ETHIOPIA, 4th Edition, 2021
41. Fitts W, Vogel AC, Mateen FJ. The changing face of osmotic demyelination syndrome: a retrospective, observational cohort study. Neurology: Clinical Practice. 2021 Aug;11(4):304-10.
42. Edelman IS, Leibman J, O'meara MP, Birkenfeld L. Interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. The Journal of clinical investigation. 1958 Sep 1;37(9):1236-56.
43. Imai, N., Osako, K., Kaneshiro, N. et al. Seasonal prevalence of hyponatremia in the emergency department: impact of age. BMC Emerg Med 18, 41 (2018). https://doi.org/10.1186/s12873-018-0182-5
44. Huwyler T, Stirnemann J, Vuilleumier N, Marti C, Dugas S, Poletti P-A, Sarasin FP, Rutschmann OT. Profound hyponatremia in the emergency department: seasonality and risk factors. Swiss Med Wkly . 2016 Dec. 18. https://doi.org/10.4414/smw.2016.14385
45. Kumar S, Pratima K, Bhattacharya R, Ambedkar SN, Saini RP. Hyponatremia in sepsis and its association with SOFA score: An observational cross sectional study. J Med Sci Res. 2023; 11(1):10-15. DOI: http://dx.doi.org/10.17727/JMSR.2023/11-3
46. Nigro, Nicole & Winzeler, Bettina & Suter, Isabelle & Schuetz, Philipp & Arici, Birsen & Bally, Martina & Blum, Claudine & Bingisser, Roland & Bock, Andreas & Huber, Andreas & Müller, Beat & Nickel, Christian & Christ-Crain, Mirjam. (2015). Symptoms and Characteristics of Individuals with Profound Hyponatremia: A Prospective Multicenter Observational Study. Journal of the American Geriatrics Society. 63. 10.1111/jgs.13325. http://dx.doi.org/10.1111/jgs.13325

47. WEISSMAN PN, SHENKMAN L, GREGERMAN RI: Chlorpropamide hyponatremia. N Eng! J Med 284:65—71, 1971
48. STORMONT JM, WATERHOUSE C: The genesis of hyponatremia associated with marked overhydration and water intoxication. Circulation 24:191—203, 1961
49. WEINER MW, EPSTEIN FH: Signs and symptoms of electrolyte disorders, in Clinical Disorders of Fluid and Electrolyte Metabolism, edited by Maxwell Ml-!, Kleeman CR, New York, McGraw-Hill Book Company, 1972, pp. 629—661
50. ARIEFF Al, LLACH F, MASSRY SG: Neurological manifestations and morbidity of hyponatremia: Correlation with brain water and electrolytes. Medicine (Baltimore) 55:121—129, 1976
51. DEMANET JC, BONNYNS M, STEVENS-ROCKMANS C: Coma Due to water intoxication in beer drinkers. Lancet 2:1115—1117, 1971
52. SWANSONG, IsERIOA: Acute encephalopathy due to water intoxication. N Eng! J Med 258:83 1—834, 1958
53. SCOTT JC, WELCH JS, BERMAN IB: Water intoxication and• sodium depletion in surgical patients. Obsie: Gynecol 26:168—175, 1965 84.
54. SAPHIR W: Chronic hypochloremia simulating psychoneurosis. JAMA 129:510—512, 19451—834, 1958
55. Adrogué HJ, Tucker BM, Madias NE. Diagnosis and Management of Hyponatremia: A Review. JAMA. 2022;328(3):280–291. doi:10.1001/jama.2022.11176
56. Ayus JC, Caputo D, Bazerque F, Heguilen R, Gonzalez CD, Moritz ML. Treatment of hyponatremic encephalopathy with a 3% sodium chloride protocol: a case series. Am J Kidney Dis. 2015 Mar;65(3):435-42. doi: 10.1053/j.ajkd.2014.09.021. Epub 2014 Nov 25. PMID: 25465163.
57. Nagase, K., Watanabe, T., Nomura, A. et al. Predictive correction of serum sodium concentration with formulas derived from the Edelman equation in patients with severe hyponatremia. Sci Rep 13, 1783 (2023). https://doi.org/10.1038/s41598-023-28380-y
58. Roe T, Brown M, Watson AJR, Panait BA, Potdar N, Sadik A, Vohra S, Haydock D, Beecham R, Dushianthan A. Intensive Care Management of Severe Hyponatremia-An Observational Study. Medicina (Kaunas). 2024 Aug 29;60(9):1412. doi: 10.3390/medicina60091412. PMID: 39336453; PMCID: PMC11434366.
59. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G. Treatment of chronic hyponatremia in rats by intravenous saline: comparison of rate versus magnitude of correction. Kidney Int. 1992; 41: 1662-1667.
60. Verbalis JG, Martinez AJ. Neurological and neuropathological sequelae of correction of chronic hyponatremia. Kidney Int. 1991; 39: 1274- 1282.
61. Tzamaloukas AH, Malhotra D, Rosen BH, Raj DS, Murata GH, Shapiro JI. Principles of management of severe hyponatremia. J Am Heart Assoc. 2013; 2: 005199.
62. Gross P, Riemann D, Henschkowski J, Damian M. Treatment of severe hyponatremia: conventional and novel aspects. J Am Soc Nephrol. 2001; 17: 10-14.
63. Al-Salman J, Kemp D, Randall D. Hyponatremia. West J Med. 2002; 176: 173-176.
64. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases. Ann Intern Med. 1987; 107: 656-664.
65. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000; 342: 1581- 1589.
66. MacMillan, T. (2023). "Osmotic demyelination syndrome in patients hospitalized with hyponatremia." NEJM Evid 2.

67. Berl T. Treating hyponatremia: damned if we do and damned if we don’t. Kidney Int. 1990; 37: 1006-1018.
68. Geoghegan, P., et al. (2015). "Sodium Correction Practice and Clinical Outcomes in Profound Hyponatremia." Mayo Clinic Proceedings 90(10): 1348-1355.
69. Anissa Pelouto, Julie C Refardt, Mirjam Christ-Crain, Adrienne A M Zandbergen, Ewout J Hoorn, Overcorrection and undercorrection with fixed dosing of bolus hypertonic saline for symptomatic hyponatremia, European Journal of Endocrinology, Volume 188, Issue 3, March 2023, Pages 322–330, https://doi.org/10.1093/ejendo/lvad028
70. Turkmen E, Karatas A, Altindal M. Factors affecting prognosis of the patients with severe hyponatremia. Nefrología. 2022;42(2):196-202.

Annex : data collection tool

	Date		
1	Age in years		
2	Sex		
3	Principal diagnosis		
4	Known comorbidities		
5	Acute symptoms Nausea and vomiting Confusion Headache Drowsiness Coma/altered GCS Seizures	Yes	No
6	Chronic symptoms Weakness Vertigo History of falls		
7	Serum sodium level initially day 1 day 2		
8	Initial serum potassium level Less than 3.5 3.5 to 5.5 Greater than 5.5		
9	Initial RFT Creatinine BUN		

10	Total amount of locally made 3% salt intake (per tsp) Day 1 Day 2		
12	Correction rate (per-anticipation)		
13	Is there a diagnosis of ODS by the treating physician after hyponatremia treatment		
14	After treatment initiated does patient have this symptoms? Vomiting Diarrhea Deterioration in consciousness Convulsion Abnormal posturing or movement Nystagmus		
15	Length of stay (discharge time duration)		
16	Death within hospital		

Declaration

I agree to accept all responsibilities for the scientific and ethical conduct of the research project. I will provide a timely progress report to my advisor and seek the necessary advice and approval from my primary advisors in the course of the research. I will communicate timely to my advisors and all stakeholders involved in the study including any source of funding for this research.

Name of the student: _____

Signature: _____

Date: _____

Approval of the Primary Advisor

Name of the primary advisor: _____

Signature: _____

Date: _____

Approval of the Co-Advisor

Name of the primary advisor: _____

Signature: _____

Date: _____