“CLINICAL PROFILE OF HYPONATREMIA IN ADULT PATIENTS ADMITTED TO MEDICAL INTENSIVE CARE UNIT OF A TERTIARY CARE HOSPITAL”

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ENDORSEMENT

This is to certify that the dissertation entitled **"CLINICAL PROFILE OF HYPONATREMIA IN ADULT PATIENTS ADMITTED TO MEDICAL INTENSIVE CARE UNIT OF A TERTIARY CARE HOSPITAL"** is a bonafide research work done by **CANDIDATE REG NO. BG0113012.**

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LIST OF ABBREVIATIONS USED

AQP-2	-	Aquaporin-2
ADH	-	Antidiuretic hormone
ALI	-	Acute lung injury
ARDS	-	Acute respiratory distress syndrome
AVP	-	Arginine vasopressin
cAMP	-	Cyclic adenosine monophosphate
CNS	-	Central nervous system
CREB	-	Cyclic adenosine monophosphate responsive element-binding
CSF	-	Cerebrospinal fluid
CVS	-	Cardiovascular system
½DNS	-	5% dextrose in half-normal saline
D5W	-	5% dextrose in water
e.g.	-	For example
ED	-	Emergency Department
ENaC	-	Epithelial sodium channel
ERK	-	Extracellular signal-regulated kinase
ESR	-	Erythrocyte sedimentation rate
GI	-	Gastrointestinal
H/O	-	History of
i.e.	-	That is,
ICU	-	Intensive care unit
IgG	-	Immunoglobulin G
LFT	-	Liver function test

m/s	-	Meters per second
MDMA	-	Methylenedioxymethamphetamine
mEq/l	-	Milli equivalents per litre
mEq/L/h	-	Milli equivalents per litre per hour
mg	-	Milligrams
mg/dL	-	Milligrams per deciliter
MICU	-	Medical intensive care unit
mL	-	Milli Litre
mL/kg/h	-	Milliliter per kilogram per hour
mmol/l	-	Millimole per litre
mOsm/kg	-	Milliosmole per Kilogram
MV	-	Mechanical ventilation
MVB	-	Multi-vesicular bodies
n	-	Total number
Na^+	-	Sodium
No.	-	Number
OTC	-	Over-the-counter
p	-	Probability
PKA	-	Protein kinase A
PNa	-	Plasma sodium
SD	-	Standard deviation
SIADH	-	Syndrome of inappropriate antidiuretic hormone
SNARE	-	Soluble N-Ethylmaleimide sensitive factor attachment receptor
SSRIs	-	Selective serotonin reuptake inhibitors

TB	-	Tuberculosis
TBW	-	Total body water
TSH	-	Thyroid-stimulating hormone
U.S.	-	United States
USA	-	United States of America
UT-A1	-	Urea transporter A1
V1a	-	Vasopressin 1a receptor
V1b	-	Vasopressin 1b receptor
V2R	-	Vasopressin 2 receptor

ABSTRACT

Background and objectives

Hyponatremia is the most common electrolyte disorder in critically ill patients and is a leading cause of morbidity and mortality. This study was done to evaluate the clinical features, etiology and severity of hyponatremia in critically ill patients admitted to Medical Intensive Care Unit.

Methodology

The present one year cross sectional observational study was done in the Department of Medicine of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients admitted in MICU with moderate to severe hyponatraemia from January 2014 to December 2014 were studied.

Results

The male to female ratio was 1.43:1 with 59% of the patients being males. Most of the patients were aged between 61 to 70 years (29%) and mean age was 58.94 ± 16.10 years. The commonest presentation was vomiting (28%) followed by confusion (26%). Nearly half of the study population had altered sensorium (48%). The commonest system to be involved was central nervous system (43%). On the basis of volume status, 50% of patients were euvolemic. 54% of the patients had severe hyponatraemia with confusion being significantly high in such patients ($p<0.001$). The commonest cause of hyponatremia was SIADH (46%) with infections (Tuberculosis, found in 57.7%) being the predominant cause. Majority (94%) of the patients in the study improved. There was positive

association between SIADH and euvolemic hypoosmolar hyponatremia ($p<0.001$) and high urine sodium ($p<0.001$).

Conclusion

Clinicians need to be aware about the common occurrence of hyponatremia, its early identification and its association with large variety of diseases. Patients with hyponatraemia should be meticulously screened for the presence or absence of tuberculosis. A thorough understanding of the pathophysiological process of hyponatremia and its associated risk factor is of great important in prompt and effective treatment.

Keywords

Hyponatraemia; Severe hyponatraemia; Serum sodium;

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INTRODUCTION

Sodium is the principal extracellular cation and the main salt of osmolality.[1] Majority of the body's sodium is found in blood plasma and other extracellular fluids, 40% in bone, and remaining 2% - 5% in other cells and organs. This asymmetric distribution of sodium is essential for life and aids in nerve conduction, passage of various nutrients into the cell and maintenance of blood pressure. Sodium related disorders (both hyponatremia and hypernatremia) are associated with considerable morbidity and mortality.[2]

Hyponatremia is the commonest electrolyte disorder,[3] reported in upto 6% of hospital patients.[4] Mild hyponatremia (plasma sodium 125-135 mmol/l) is found in as many as 15 to 30% of hospitalized patients, with an average of about 25% of intensive care unit (ICU) patients experiencing this disorder. The occurrence and consequences of hyponatremia increases with age. Hyponatremia that is moderate to severe (plasma sodium 125 and below), and particularly of rapid onset is often associated with substantial morbidity and mortality.[5]

Despite the awareness on hyponatremia since long time, this common disorder remains an enigma due to its association with a plethora of underlying disease states, and its multiple etiologies with differing pathophysiological mechanisms.

Hyponatremia, which is defined as plasma sodium concentration of less than 135meq/L, occurs primarily due to imbalance in water homeostasis, antidiuretic hormone (ADH) regulation and renal handling of filtered sodium. The two most

common causes are effective circulating volume depletion causing non- osmotic release of ADH and the syndrome of inappropriate ADH secretion, disorders in which ADH secretion is not suppressed despite decrease in plasma osmolality.[6]

SIADH, a common cause of hyponatremia, is associated with many clinical conditions. These include neoplasia (pulmonary, mediastinal and extrathoracic tumours), central nervous system disorders (inflammatory or demyelinating diseases, stroke and trauma), drugs and pulmonary diseases (infections, acute respiratory failure, and positive pressure ventilation). Tuberculosis, one of the common illnesses in developing countries like India, can present with various clinical manifestations including non-specific symptoms of hyponatremia. Tuberculosis can induce hyponatremia via several mechanisms such as local invasion to the adrenal gland (leading to adrenal insufficiency), local invasion of hypothalamus or pituitary gland, TB meningitis and inappropriate ADH secretion via pulmonary infections.[7,8]

Alterations in water and sodium balance can affect the central nervous system. Some of these patients with clinically significant hyponatremia may present with non-specific or neurological symptoms due to cerebral edema.[9] The clinical manifestations of hyponatremia are more evident when the decrease in serum sodium concentration is large or when the decrease occurs rapidly. Patients with serum sodium concentration greater than 125 mEq/l are usually asymptomatic, whereas those in whom these values are lower may have symptoms that include headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, and depressed reflexes. Severe and rapidly evolving hyponatremia may present with seizures, coma, permanent brain damage, respiratory arrest, brainstem herniation and death.[10]

The Emergency Department physician should have an increased index of suspicion of hyponatremia in patients with pneumonia; active tuberculosis; pulmonary abscess; neoplasm; asthma; or in patients with CNS infection, trauma, or neoplasm. The patient's medication list should be examined for drugs known to cause hyponatremia. A history of hypothyroidism or adrenal insufficiency should be sought because each is associated with hypo-osmolar hyponatremia.[10]

Physical findings are highly variable and dependent on the degree and the chronicity of hyponatremia. Patients with acutely developing hyponatremia are symptomatic at a level of 120 mEq/L while patients with chronic hyponatremia can tolerate lower levels. Patients could present with variable degrees of cognitive impairment (eg, difficulty with short term recall; loss of orientation to person, place, or time; frank confusion or depression), focal or generalized seizure activity, signs of brainstem herniation including coma; fixed, unilateral, dilated pupil; decorticate or decerebrate posturing; and respiratory arrest.[10]

In addition to neurologic findings, patients may exhibit signs of hypovolemia or hypervolemia. Determining the hydration status of the patient may help establish the etiology of the hyponatremia and suggest the best treatment course.[10]

Dry mucous membranes, tachycardia, diminished skin turgor, and orthostasis suggest hypovolemic hyponatremia which could be due to excessive loss of body fluids and replacement with inappropriately dilute fluids.[10]

Pulmonary rales, S3 gallop, peripheral edema, or ascites suggest hypervolemic hyponatremia due to excess retention of sodium and free water (e.g. cirrhosis of liver, nephrotic syndrome, congestive heart failure).[10]

Patients who lack findings of hypovolemia or hypervolemia are considered to have euvolemic hyponatremia, which is consistent with etiologies such as exogenous free water load, hypothyroidism, cortisol deficiency, or syndrome of inappropriate antidiuretic hormone (SIADH).[10,11]

Early diagnosis and treatment can prevent complications such as worsening condition of the neurological status, prolonged hospital stay and mortality.[12]

Distinguishing the causes of hyponatremia can be challenging in clinical practice. The clinical presentations of severe hyponatremia can range from mild nonspecific symptoms such as nausea, headache, and lethargy, to severe symptoms causing seizure and coma. The data available on clinical presentation and etiology is scarce in Indian ICU settings, especially in those patients who develop moderate to severe hyponatremia. Hence, the present study was undertaken to assess the clinical profile and etiology of clinically significant hyponatremia which will help not only to treat the patients, but most importantly avoid further morbidity and mortality.

OBJECTIVES

Aims

This study was aimed to assess the clinical features, etiology and severity of hyponatremia in critically ill patients admitted to MICU.

Objectives

The objectives of the present study were:

1. To study clinical features of hyponatremia in adult patients admitted to MICU.
2. To find the etiology of hyponatremia in hospitalized patients under MICU settings.
3. To classify the severity of hyponatremia among the patients admitted to MICU.

REVIEW OF LITERATURE

Critical care – An overview

Since the first intensive care units (ICUs) were established in the United States in the 1960s, there has been a gradual growth in the appreciation of the importance and magnitude of critical illness. The frequency of critical illness and the provision of critical care services have now reached epidemic proportions. Of the 38 million annual U.S. hospital admissions of children and adults,[13] nearly 6 million, or 2% of the U.S. population, are admitted to an ICU.[14] The disease burden of the disorders and conditions that constitute critical illness is of sufficient scale, so efforts are needed to prevent and treat these disorders to have implications on overall public health.[15]

Critically ill patients have been defined as those that by dysfunction or failure of one or more organs/systems require interventions for monitoring and therapy.[16] They may require immediate form of organ support, (intubation, ventilation, inotropes) or are likely to suffer an acute cardiac, respiratory or neurological deterioration, requiring such support.[17]

Critical illness consists of a heterogeneous group of conditions and disorders that share a risk of organ dysfunction, long-term morbidity, and mortality. The syndromes that mostly requires critical care include sepsis, acute respiratory distress syndrome [ARDS] / acute lung injury [ALI], and organ failure.[15]

The provision of mechanical ventilation (MV) for acute respiratory failure was a major motivating factor in the development of ICUs and is one of the hallmarks of critical care.[15]

The clinical epidemiology of critical illness is vital in order to form meaningful patient-oriented research, and health policy in critical care. Describing the natural history of disease helps in development of treatment plans and improves outcomes and the care delivered at the bedside. Understanding the burden of disease influences the prioritization of research efforts and the allocation of health care resources. Knowledge of risk factors for disease aids in prevention of disease, timely intervention and selection of study populations.[15]

ICUs are the units with the highest mortality in hospital. Mortality rates in ICUs range between 16% and 67% depending on the patient characteristics. Critically ill patients have a high prevalence of electrolyte disorders because of the presence of multiple causative factors. Early diagnosis and treatment is necessary. Clinicians should be cautious about electrolyte homeostasis and the underlying pathophysiology of electrolyte disorders to provide optimal therapy for patients.[18]

Fluid and electrolyte disorders are among the most common clinical problems encountered in the setting of intensive care. Critical disorders such as severe burns, trauma, sepsis, brain damage, and heart failure lead to disturbances in fluid and electrolyte homeostasis. Possible mechanisms include reduced perfusion to the kidney due to hypovolemia or hypotension; activation of hormonal systems such as renin-angiotensin-aldosterone system and vasopressin; and tubular damage caused by ischemic or nephrotoxic kidney damage, including renal insult caused by

a myriad of medications used in the intensive care. In addition, inappropriate administration of fluid and electrolytes should be considered in the diagnosis and treatment of fluid and electrolyte disturbances.[19]

Disturbances in plasma sodium concentrations are a common clinical problem in patients admitted to the intensive care unit. Many cases of dysnatremia are acquired after a patient is admitted to the ICU, and the presence of dysnatremia is associated with poor prognosis. A recent study involving 151,486 adult patients from 77 intensive care units over a period of 10 years has demonstrated that many cases of dysnatremia are acquired in the intensive care unit, and that the severity of dysnatremia is associated with poor outcome in a graded fashion.[20] Another study on the ICU patients with dysnatremias corroborated these findings, reporting that ICU-acquired hyponatremia and ICU-acquired hypernatremia were associated with increased mortality.[21]

Hyponatremia

Definition

Hyponatremia is defined as a serum sodium level of less than 135 mEq/L. The most severe form of hyponatremia is that in which the serum sodium level is less than 120 mEq/L. Moderate hyponatremia is 120 to 130 mEq/L, and mild hyponatremia (although that can be a definition that is elusive because, indeed, that is still hyponatremia) is 131 to 135 mEq/L.[22]

Low plasma [Na^+] represents a relative water excess in conjunction with impaired ability of the kidney to excrete electrolyte-free water. Removal of excess

water by the kidney requires urinary dilution, which is compromised in virtually all patients in the ICU:[23]

1. Heart failure, sepsis, shock, and multiple organ dysfunction syndrome impair glomerular filtration and enhance sodium and water reabsorption at the proximal tubule, thereby diminishing delivery of the filtrate to the diluting segment, i.e., the thick ascending limb of the loop of Henle and the distal convoluted tubule;

2. Loop diuretics, thiazides, osmotic diuretics, and tubulointerstitial pathology reduce the reabsorption of sodium and chloride in the diluting segment;

3. Nonosmotic stimuli for vasopressin production such as pain, nausea, medications, and hypovolemia lead to increased water reabsorption in the collecting duct. In addition to impaired urinary dilution, hyponatremia in the critical care setting is related to inappropriate administration of hypotonic fluid.

Symptoms of hyponatremia occur most commonly with a rapid decrease in plasma [Na^+] to < 125 mEq/L. Seizure and coma usually result from rapid decrease in plasma [Na^+] to < 110 mEq/L. The most dreaded complication in a patient with symptomatic hyponatremia is acute cerebral edema. Risk factors for development of acute cerebral edema should be identified before initiating therapy, including hypoxia, postoperative premenopausal women, elderly women on thiazide diuretics, polydipsic patients, children, and marathon runners.[24] Symptoms of hyponatremia may not be apparent in ventilated and sedated patients in the ICU, and worsening of

cerebral edema may lead to catastrophic consequences such as brainstem herniation and respiratory arrest.[19]

The time of development of hyponatremia and the presence of symptoms should dictate the management of hyponatremia. Correction of plasma [Na^+] should be undertaken without delay in symptomatic patients, particularly those experiencing seizures. Development of hyponatremia in less than 48 hours and the presence of symptoms strongly suggest that the benefit of treating acute cerebral edema outweighs the risk of treatment-associated adverse effects. Hypertonic sodium chloride with or without a loop diuretic is usually started at a rate of 1-2 mL/kg/hr to raise sodium concentration by 1-2 mEq/L/hr. This rapid correction of hyponatremia should be limited to the initial phase of management. The overall correction of [Na^+] should not exceed 8-12 mEq/L for 24 hours, as the risk of osmotic demyelination rises above this limit.[19]

Estimated change in plasma [Na^+] following the administration of 1 L of an intravenous fluid regimen can be calculated by equations proposed by Madias and Adrogue as follows:[19]

$$\text{Change in plasma } [Na^+] = \frac{\text{Infusate } [Na^+] - \text{plasma } [Na^+]}{\text{Total body water} + 1}$$

$$\text{Change in plasma } [Na^-] = \frac{\text{Infusate } [Na^-] + \text{infusate } [K^+] - \text{plasma } [Na^+]}{\text{Total body water} + 1}$$

These equations have been shown to accurately predict changes in plasma [Na^+] under most clinical settings with a tendency to underestimate the achieved plasma [Na^+], sometimes by significant amounts.[7,25] An important caveat to be

remembered is that these equations assume human body as a closed system and therefore do not take into account ongoing fluid and electrolyte gain or loss. Thus, a cornerstone of therapy is close monitoring of symptoms, amount of fluid given to the patient, urine output, and plasma and urine electrolytes.[19]

Prevalence

Worldwide

Hyponatremia involves up to 3 to 6 million persons in the US annually. It can affect 15% to 30% of hospitalized patients, with an average of about 25% of intensive care unit (ICU) patients in most studies that have been done.[26,27]

Hoorn et al[28] found a 30% overall incidence of PNa less than 136mmol/l and a 38% incidence in the ICU. Severe hyponatremia, PNa less than 125, was present in 3% of hospitalized patients and occurred during hospitalization in half of the cases. Importantly, hospital acquired cases of severe hyponatremia were not recognized or treated as promptly as were cases present on admission.

Stelfox et al.[**21**] reported ICU acquired hyponatremia (defined as a SNa less than 133 mmol/l) in 11% of patients and that this was associated with an increase in in-hospital mortality from 16 to 28%. The population studied included medical, surgical, trauma, and neurologic patients.

A study performed by Sherlock et al.[29] in 2006 confirmed that 56% of patients with SAH were hyponatremic

Funk et al[20] defined borderline, mild, and severe hyponatremia as 130–135mmol/l, 125–129, and greater than 125, respectively. They found an overall

incidence of hyponatremia in 17.7% of ICU admissions with a breakdown of 13.8% classified as borderline, 2.7% mild, and 1.2% severe.

Mulliy et al.[30] in a study titled "Hyponatremic Emergencies" found that hyponatremia is present in 7 - 32% of patients with meningitis.

A study by Waikar SS et al[31] in 2009, examined data from approximately 98,000 adults and children, admitted to two large teaching hospitals found an initial PNa of less than 135 mmol/l in 14.5% and that an additional 5.2% acquired hyponatremia during their hospitalization. Of these, hyponatremia resolved in 7.2%, developed in 3.8%, and persisted in 8.6%. Mild hyponatremia (defined as 130–134 mmol/l) accounted for the majority of the cases (83%), moderate (120–130mmol/l) for 16.8%, and severe (<120mmol/l) for 0.2%. Compared with normonatremia, hospital- acquired and persistent hyponatremia each conferred an approximately three-fold increase in in-hospital mortality. There was no sex difference in the incidence of hyponatremia, but women were more likely to have severe hyponatremia. Patients with the most severe hyponatremia did not have a statistically increased mortality rate 1.46 (0.73–2.91), a surprising observation.

A recent study by Chitsazian Z. et al.[32] to evaluate the prevalence of hyponatremia in 95 brain injury patients hospitalized in the intensive care unit (ICU) in Kashan Shahid-Veheshti hospital reported prevalence of hyponatremia as 31.6%. This study revealed no meaningful differences between age, sex, underlying disease and the prevalence of hyponatremia.

India

Nandani Chatterjee et al,[33] in a study conducted for a period of 1 year in tertiary care hospital in Eastern India reported total number of patients admitted as 1221, out of them 201 patients i.e. 16.4% had a serum Na of <135mEq/L. The most common underlying predisposing factor for hyponatremia was gastro-intestinal fluid loss followed by cerebrovascular accidents and pulmonary sepsis.

Mahavir Agarwal et al,[34] in a comparative study of the clinico-etiological profile of hyponatremia at presentation with developing in-hospital, concluded confusion (14%), headache(40%) and malaise(38.6%) as the common symptoms. Decreased intake followed by increased losses were concluded as the most common mechanisms. 31.4% developed hyponatremia during their stay in the hospital. Drugs, Fluid overload and inappropriate Ryle's tube feeding more commonly precipitated hyponatremia.

Miyashita J et al,[35] in study on impact of hyponatremia and SIADH on mortality in critically ill patients with aspiration pneumonia concluded that hyponatremia due to SIADH was strongly associated with increased mortality in critically ill patients. 29% of 221 patients had hyponatremia. Of these 95% were hypotonic hyponatremia which were further assessed as having hypervolemic(63%), hypovolemic(5%) and euvolemic(32%) hyponatremia. Of the euvolemic patients,70% had SIADH. Hyponatremia due to SIADH was associated with increased 30 days mortality.

Thomas Vurgese et al.[36] in a study done on frequency and etiology of hyponatremia in adult hospitalized patients in medical wards of a general hospital,

the commonest cause of hyponatremia was concluded as SIADH due to pneumonia. Overall incidence of hyponatremia was 3.6%. Out of these 56% were males and 44% were females. The commonest age group affected was 45-64 years. The mean serum sodium levels were 122mmol/L in 59% patients.

Recently, Padhi R et al. ascertained frequency, predisposing conditions and outcome in critically ill patients with hyponatremia on intensive care unit (ICU) admission at Institute of Medical Sciences and SUM Hospital, Bhubaneswar, Odisha, India. In the hyponatremic group, the frequency of hyponatremia on ICU admission was 34.3%, most were euvolumic (58.96%). Females comprised 36.5%; The mean age was 60.4 ± 17.2. The Syndrome of inappropriate Antidiuretic Hormone (SIADH) criteria was met in ninety-one patients (36.25%), pneumonia being the leading cause of SIADH. Patients with severe sepsis, elective surgery patients, renal failure and heart failure, cirrhosis of liver and subarachnoid hemorrhage were other more likely etiologic causes ($P < 0.05$).[37]

Age

The incidence of hyponatremia is much more in the elderly mainly owing to impaired ability to maintain water and electrolyte homeostasis in response to dietary and environmental changes.[38]

Sex

Chronic hyponatremia in postmenopausal women is common.[39] Studies have shown that female gender is an important risk factor for the development of severe complications. 60% of the cases in a prospective study on hyponatremia by Clayton et al were females.[38]

Categories

Hyponatremia has many causes that are subdivided based on the patient's volume status.

Categories of hyponatremia[40]

Pseudohyponatremia • Hyperglycemia • Hyperlipidemia • Hyperproteinemia (multiple myeloma, macroglobulinemia) • Laboratory or blood draw errors

Hypovolemic hyponatremia (decreased TBW and sodium, with a relatively greater decrease in sodium)
• Body fluid losses
  o Sweating, vomiting, diarrhea, GI suction
• Third spacing
  o Bowel obstruction, burns
• Renal causes
  o Diuretics, mineralocorticoid deficiency, osmotic diuresis, renal tubular acidosis, salt-wasting nephropathies

Hypervolemic hyponatremia (increased total body sodium with a relatively greater increase in TBW) • Heart failure • Chronic renal failure • Hepatic failure/cirrhosis
Euvolemic hyponatremia (increased TBW with near-normal total body sodium) • SIADH • Drugs causing SIADH, including diuretics, barbiturates, carbamazepine, chlorpropamide, clofibrate, opioids, SSRIs, tolbutamide, vincristine • Psychogenic polydipsia • Beer potomania • Hypothyroidism • Adrenal insufficiency • MDMA (ecstasy) • Accidental or intentional water intoxication

Pseudohyponatremia

In pseudohyponatremia, serum sodium levels may be artificially low due to increased levels of plasma proteins or lipids or due to increased serum concentrations of osmotically active chemicals such as glucose and mannitol.[41] The phenomenon of pseudohyponatremia is explained by the increased percentage of large molecular particles relative to sodium. These large molecules do not contribute to plasma osmolality (resulting in a state in which the relative sodium concentration is decreased), but the overall osmolality remains unchanged. In addition, emergency clinicians should always consider blood draw or laboratory errors as a possible etiology of a patient's hyponatremia, especially if the blood sample was drawn near an infusion site using D5W (5% dextrose in water) or ½DNS (5% dextrose in half-normal saline) or when a very abnormal sodium level is reported in an otherwise healthy patient.[40]

Hyperglycemia is sometimes considered a cause of pseudohyponatremia; however, it actually causes a dilutional hyponatremia by pulling water into the vascular space by osmosis, as glucose is osmotically active. One formula that is commonly used to correct serum sodium levels based on the degree of a patient's hyperglycemia advocates adding 1.6 mEq/L to the measured sodium for every 100 mg/dL rise of glucose above 100mg/dl for up to about 400mg/dl, then 4 mEq/L should be added for every additional 100 mg/dL.[42]

It may be easier for a busy emergency clinician to remember that the maximum fall for every 100 mg elevation in blood glucose is about 2.0 to 2.5 mEq/L of sodium.[40]

Hypovolemic Hyponatremia

It is hyponatremia that occurs with dehydration when there is decreased extracellular volume combined with an even greater loss of sodium. Hyponatremia secondary to body fluid losses must be differentiated from low sodium secondary to renal losses. Body fluid losses include vomiting, diarrhea, sweating, gastrointestinal suction, and "third spacing," as in patients with bowel obstruction, burns, or intra-abdominal sepsis. Hypovolemic hyponatremia due to renal causes includes diuretic use, mineralocorticoid deficiency, renal tubular acidosis, and salt-wasting nephropathy. Hypovolemic hyponatremia can be further exacerbated when fluid losses are replaced with hypotonic saline. Clues to the underlying cause of hypovolemic hyponatremic dehydration may be obtained by evaluating the patient's serum bicarbonate, chloride, and potassium levels. Hyponatremic patients who have concomitant hypochloremia, alkalosis, and hypokalemia likely have hyponatremia due to protracted vomiting or prolonged gastric suction. A normal gap metabolic acidosis should alert emergency clinicians that diarrhea may be the cause of a patient's dehydration and hyponatremia. Hyperkalemia with a normal gap acidosis may be an important clue to an underlying diagnosis of adrenal insufficiency.[40]

Hypervolemic Hyponatremia

Hypervolemic hyponatremia is hyponatremia with increased extracellular volume. It occurs when sodium and water are retained but water retention exceeds sodium retention. On physical examination, most of these patients present with edema. Hyponatremia with increased total body sodium occurs in patients with congestive heart failure, chronic renal failure, and hepatic failure secondary to

hypoperfusion of the kidneys, causing high aldosterone secretion and decreased free water excretion.[40]

Euvolemic Hyponatremia

The final category of hyponatremia includes patients who are euvolemic but have increased total body water (TBW). The most common causes of this type of hyponatremia include SIADH, psychogenic polydipsia,[43] beer potomania,[44] hypothyroidism, diuretic use in patients with mild congestive heart failure, and accidental or intentional water intoxication. These patients do not present with edema because most of the increased body water is intracellular and not intravascular. Patients prescribed various psychiatric medications including selective serotonin reuptake inhibitors (SSRIs) and carbamazepine can develop hyponatremia. The mechanism by which SSRIs cause hyponatremia is thought to be secondary to development of SIADH. Hyponatremia without edema has also been described in patients after the use of the recreational drug ecstasy (3,4-methylenedioxymethamphetamine, or MDMA).[45]

Factors that may contribute to hyponatremia following ecstasy ingestion most commonly include excessive fluid intake secondary to central polydipsia and fluid third-spacing. Beer potomania is a specific hypo-osmolality syndrome related to consumption of beer, which is poor in solutes and electrolytes.[40]

SIADH is an important cause of hyponatremia that occurs when normal control of ADH secretion is lost and ADH is secreted independent of the body's need to conserve water. The process results from excess ADH production that causes TBW to increase, diluting the body's sodium and causing the serum sodium to

decrease. The excessive release of ADH is most commonly from the posterior pituitary gland but can also be from other ectopic sources including the lung. Patients with SIADH have inappropriately concentrated urine despite the presence of a low serum osmolality and normal circulating blood volume. Patients with SIADH have excess TBW but no signs of edema, ascites, or heart failure because most of the increased body water is intracellular and not intravascular. In general, patients with SIADH have normal acid-base status, normal potassium balance, and normal adrenal function.[40]

The 3 most common causes of SIADH are as follows:[40]

- Pulmonary lung masses and infections
- Central nervous system disorders,
- Drug use.

Lung cancers (especially small cell cancer), pneumonia, and tuberculosis can lead to SIADH. Central nervous system infections, masses, and psychosis can also cause SIADH. There are a large number of medications associated with SIADH, the most common of which are thiazide diuretics, narcotics, lithium, oral hypoglycemics, barbiturates, antineoplastics, and antiepileptics.[40]

The Pathophysiology of Hyponatremia

Water Balance Regulation: The Brain–Kidney Connection

Water balance regulation depends on an interaction between specialized sensors that translate the signals they receive (high serum osmolality, low effective circulating volume) to the central release of arginine vasopressin (the antidiuretic

hormone) into the circulation, which then stimulates water reabsorption in the renal collecting duct.[46] Figure 1 shows how water balance regulation is disturbed during hyponatremia, and also provides an overview of the regulatory system during normal physiology.

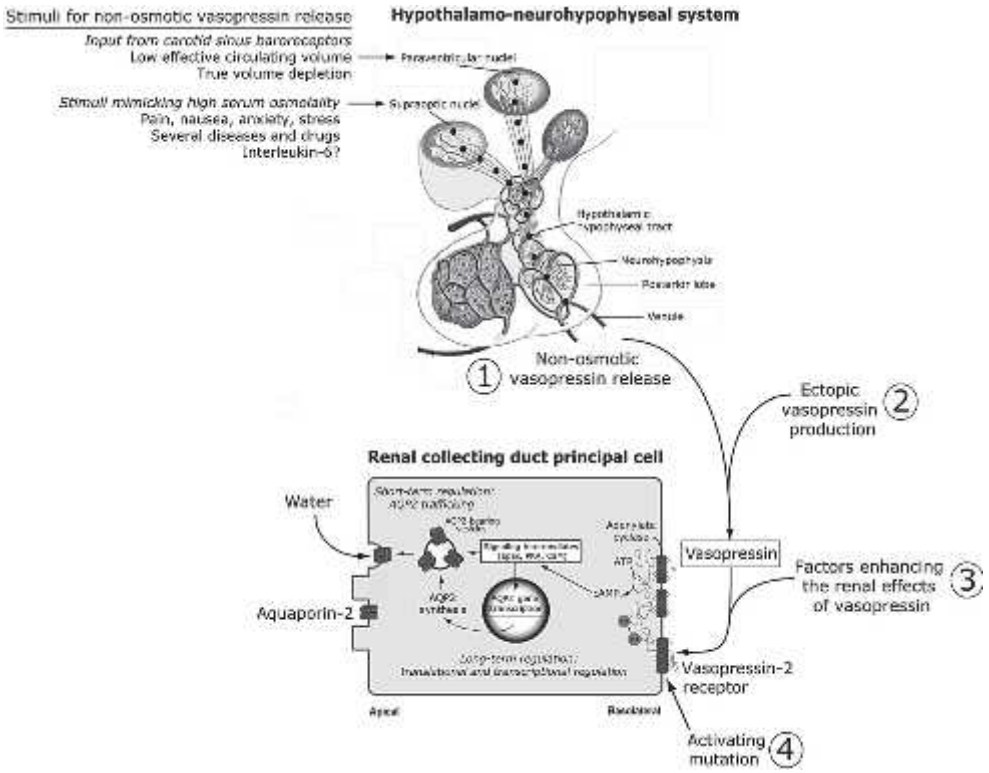


Figure 1. The pathophysiology of vasopressin during hyponatremia[46]

In the majority of patients, hyponatremia develops because vasopressin is secreted non-osmotically resulting in renal water reabsorption. The figure shows the four mechanisms that can cause this effect: (1) non-osmotic vasopressin release by the posterior pituitary induced by specific stimuli from the paraventricular or supraoptic nuclei; (2) ectopic vasopressin production; (3) factors that may enhance the renal effects of vasopressin, and, finally, (4) a vasopressin-like effect caused by an activating mutation of the vasopressin-2 receptor. In addition, details of the hypothalamo - neuro - hypophyseal system and the intracellular signaling cascade in

the renal collecting duct principal cell are shown. The illustration of the hypothalamo-neuro- hypophyseal system was adapted from Patel and Balk.[46,47]

Water balance regulation is primarily designed to control serum osmolality and to a lesser extent blood volume (vasopressin starts to rise after a 1% increment in serum osmolality vs. a 5–10% decrease in blood volume). The serum osmolality is sensed by osmoreceptors in several parts of the brain, including the supraoptic nuclei of the hypothalamus, the subfornical organ, and the organum vasculosum of the lamina terminalis.[48,49]

A rise in serum osmolality causes water to move through the water channels of the osmoreceptor cell membranes, which then causes a change in cell volume. This leads to an increase in the activity of stretch-inhibited cation channels (including the N-terminal variant of the transient receptor potential vanilloid type-1), affecting membrane voltage and ultimately the action potential discharge.[46] The accelerated action potential discharge causes an influx of calcium through a voltage-gated calcium channel which triggers a cascade of molecular events that ultimately leads to the neurosecretion of secretory vesicles containing vasopressin into the bloodstream. On the other hand, the carotid sinus baroreceptors sense a low effective circulating volume, and parasympathetic afferents transfer this signal to the vasomotor center, which increases the rate of vasopressin secretion by the cells in the paraventricular nuclei. Once released into the circulation, vasopressin can activate three types of G-coupled receptors, including V1a (vascular and hepatic), V1b (anterior pituitary), and V2 (renal collecting duct). The activation of the vasopressin 2 receptor by vasopressin stimulates an intracellular cascade, which

ultimately results in the insertion of aquaporin (AQP)-2 (AQP2) water channels in the apical membrane (fig. 2 shows this process by electron microscopy).[46]

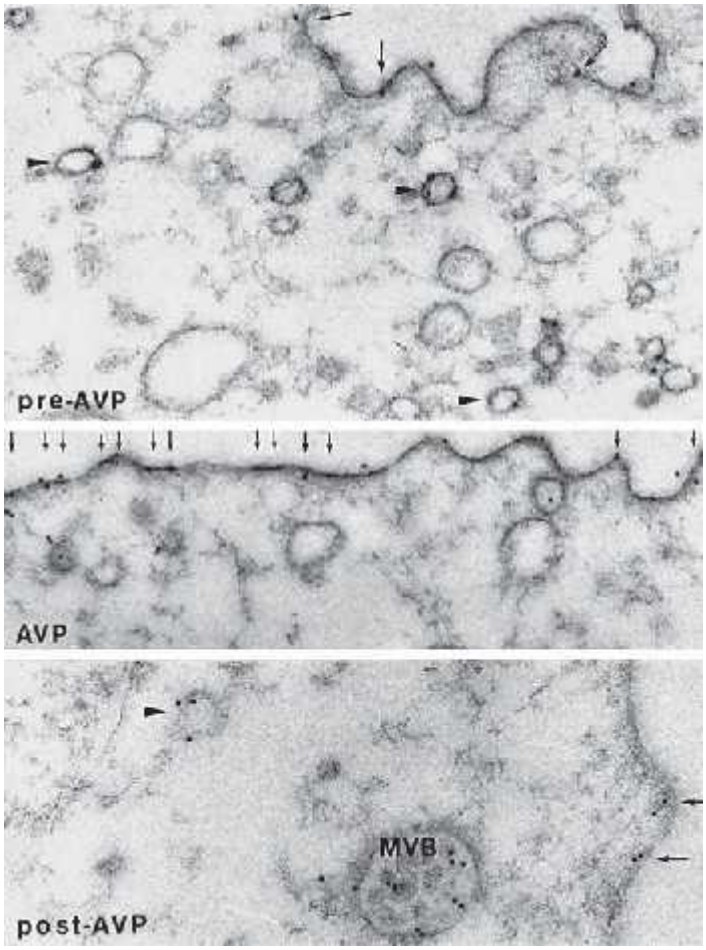


Figure 2. Immuno-gold localization of aquaporin-2 (AQP2) in renal collecting ducts before, during and after stimulation with arginine vasopressin (AVP)[46]

Electron microscopy images showing immuno-gold localization of the water channel AQP2 in isolated perfused tubules of the renal collecting duct principal cell.

A. The basal condition (pre-AVP, osmotic water permeability 65 μm/s) with AQP2 mainly localized in vesicles (arrowheads).

B. Stimulation with arginine vasopressin (AVP, osmotic water permeability 454 µm/s) and the insertion of AQP2 in the apical plasma membrane (multiple arrows) is illustrated.

C. The situation after stimulation with arginine vasopressin (post-AVP, osmotic water permeability 204 µm/s) with AQP2 again mainly localized in vesicles, including multi-vesicular bodies (MVB).[46]

The presence of AQPs in combination with an osmotic gradient allows water to move through the principal cell, returning to the basolateral bloodstream via the constitutively expressed AQP3 and AQP4 water channels.[50] Vasopressin also increases sodium and urea permeability in the collecting duct (by increasing the number of the epithelial sodium channel, ENaC, and the urea transporter, UT-A1), thereby maintaining the osmotic and medullary interstitial gradients and further stimulating antidiuresis.[51]

Short-term control of water permeability is achieved through trafficking of AQP2-containing vesicles to the apical membrane, whereas long-term control influences the abundance of the AQP2 protein. The molecular machinery of this V2R-AQP2 cascade is increasingly being unraveled. The current understanding of this cascade is that stimulation of the V2R by vasopressin activates the Gs adenylyl cyclase system, stimulating cAMP and protein kinase A (PKA), which triggers the phosphorylation of many proteins including AQP2.[50]

However, several other signaling pathways have been implicated in the V2R-AQP2 cascade, involving for example PKA-independent pathways, calcium-calmodulin, Rho, Soluble N -ethylmaleimide-sensitive factor attachment receptors

(SNARE) proteins, cAMP responsive element-binding protein (CREB) and extracellular signal-regulated kinase (ERK).[46]

Hyponatremia: Non-Osmotic Vasopressin Release and Its Escape

The presence of hyponatremia nearly always implies that vasopressin is released non-osmotically, thereby preventing the excretion of electrolyte-free water, and diluting the serum sodium concentration. For example, Anderson et al.[52] showed that non-osmotic vasopressin secretion was present in 97% of hyponatremic patients studied. Causes of non-osmotic vasopressin release include a low effective circulating volume, several diseases and drugs, and nonspecific stimuli such as anxiety, stress, pain, and nausea. Apart from the increased production of vasopressin, vasopressin can also be produced ectopically (e.g., in small cell lung cancer), its renal effects can be enhanced with normal vasopressin levels (e.g., by cyclophosphamide), or a vasopressin-like effect can occur in the absence of vasopressin (e.g., through an activating mutation of the V2R;).[53]

Although many of the pathways that influence central non-osmotic vasopressin release are unknown, there is increasing evidence for a relationship between high interleukin-6 levels and vasopressin release. Interleukin-6 appears to take the same secretory pathway as vasopressin and interleukin-6 receptors and signal-transducing units exist in the hypothalamo-neurohypophyseal system. It has been recently shown that there is a direct relationship between a rise in C-reactive protein and the development of hyponatremia, suggesting that the acute-phase response, perhaps through interleukin-6, could explain the established relationship between certain infections and hyponatremia.[46]

There may have been an evolutionary benefit for the non-osmotic release of vasopressin to conserve water during times of severe volume depletion or infection. To date, however, the non-osmotic release of vasopressin is often unwanted (for example because it is paraneoplastic or drug-related), and may give rise to the syndrome of inappropriate antidiuresis (SIAD). It is important to realize that the actual development of hyponatremia always requires the ongoing consumption of water, which in humans is often socially determined rather than thirst driven (conversely, it is difficult to induce hyponatremia in animals).[46]

However, a defense mechanism exists to limit the degree of hyponatremia when vasopressin levels are persistently high and water is ingested continuously. 'Escape' from vasopressin-induced antidiuresis is an important physiological response, during which water diuresis develops despite high circulating levels of vasopressin.[50] The renal mechanisms of vasopressin escape include not only a downregulation of AQP2 (through a combination of V2R internalization and transcriptional and translational regulation of AQP2), but also of the epithelial sodium channel ENaC and the urea transporter UT-A3, which may contribute to a solute diuresis.[54]

Clinical features

Hyponatremia can present with very vague complaints involving multiple organ systems, which leads to a broad differential diagnosis. Common complaints with mild to moderate sodium abnormalities include irritability, nausea, weakness, abdominal pain, lethargy, confusion, and tachypnea. These vague complaints can also be seen in hypothyroidism, hypoglycemia, viral illnesses, psychiatric illnesses,

and other electrolyte abnormalities. In more extreme cases of hyponatremia and hypernatremia, patients may present with head injury after a fall or a seizure, and the differential diagnosis may include seizure, polysubstance abuse, cerebrovascular accident, and cardiac emergencies.[55]

Many medical illnesses, such as congestive heart failure, liver failure, renal failure, or pneumonia, may be associated with hyponatremia. These patients frequently present because of primary disease symptomatology (eg, dyspnea, jaundice, uremia, and cough).[56]

Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, and (if severe) seizures and coma. Overt neurologic symptoms most often are due to very low serum sodium levels (usually < 115 mEq/L), resulting in intracerebral osmotic fluid shifts and brain edema. This neurologic symptom complex can lead to tentorial herniation with subsequent brain stem compression and respiratory arrest, resulting in death in the most severe cases.[55]

The severity of neurologic symptoms correlates well with the rate and degree of the drop in serum sodium. A gradual drop in serum sodium, even to very low levels, may be tolerated well if it occurs over several days or weeks, because of neuronal adaptation. The presence of an underlying neurologic disease, like a seizure disorder, or non-neurologic metabolic abnormalities, like hypoxia, hypercapnia, or acidosis, also affects the severity of neurologic symptoms.[55]

Obtaining a detailed medication history, including information on over-the-counter (OTC) drugs the patient has been using, is important because many

medications may precipitate hyponatremia (eg, antipsychotic medications, diuretics). A dietary history with reference to salt, protein, and water intake is useful as well. For patients who are hospitalized, reviewing the records of parenteral fluids administered is crucial.[55]

Diagnosis

There are three essential laboratory tests in the evaluation of patients with hyponatremia that, together with the history and the physical examination, help to establish the primary underlying etiologic mechanism. In general, the etiology of the hyponatremia directs its management. These tests are urine osmolality; serum osmolality; and urinary sodium concentration.[55]

Urine osmolality helps to differentiate between conditions associated with impaired free water excretion and primary polydipsia, in which water excretion should be normal (provided intact kidney function). With primary polydipsia, as with malnutrition (severe decreased solids intake) and a reset osmostat, the urine osmolality is maximally dilute, generally less than 100 mOsm/kg. A urine osmolality greater than 100 mOsm/kg indicates impaired ability of the kidneys to dilute the urine. This usually is secondary to elevated vasopressin (ADH) levels, appropriate or inappropriate.[55]

Serum osmolality readily differentiates between true hyponatremia and pseudohyponatremia secondary to hyperlipidemia, hyperproteinemia, or hypertonic hyponatremia. Sources of hypertonic hyponatremia include elevations of glucose; mannitol; glycine (after urologic or gynecologic procedures); sucrose and maltose (contained in IgG formulations).[55]

Urinary sodium concentration helps to differentiate between hyponatremia secondary to hypovolemia and SIADH. With SIADH (and salt-wasting syndrome), the urine sodium is greater than 20-40 mEq/L. With hypovolemia, the urine sodium typically measures less than 25 mEq/L. However, if sodium intake in a patient with SIADH (or salt-wasting) happens to be low, then urine sodium may fall below 25 mEq/L.[55]

Ancillary tests

Serum uric acid levels can be important supportive information (they are typically reduced in SIADH and also reduced in salt wasting). After correction of hyponatremia, the hypouricemia corrects in SIADH but remains with a salt-wasting process. Thyroid-stimulating hormone (TSH) and serum cortisol levels should be measured if hypothyroidism or hypoadrenalism is suspected. Serum albumin, triglycerides, and a serum protein electrophoresis also may be indicated for particular patients.[55]

Diagnostic considerations in the approach to hyponatremia[54]

- In acute and symptomatic hyponatremia, therapy precedes diagnosis
- The symptoms of hyponatremia are: nausea and vomiting (<136 mmol/l), cognitive impairment (<136 mmol/l), confusion (<131 mmol/l), seizures (<125 mmol/l), noncardiogenic pulmonary edema (<125 mmol/l), coma (<117 mmol/l), and death (depending on therapy)
- Chronic hyponatremia is also associated with other neurological impairments, such as falls, gait disturbances, and attention deficits
- Pseudohyponatremia (still possible with ion-selective electrodes) and hyperglycemia-induced hyponatremia should be considered early during the diagnostic process
- Hyponatremia usually means high vasopressin levels – the diagnostic process should focus on the reason why these levels are elevated
- The clinical assessment of the extracellular fluid volume should not be a determining factor in the differentiation of hyponatremia
- Hypopituitarism and primary adrenal insufficiency are often overlooked, the latter because hyperkalemia may be absent and random cortisol levels may be normal
- The syndrome of inappropriate antidiuresis should only be diagnosed after excluding diuretic use, thyroid, adrenal, and pituitary insufficiency
- If all else fails, calculate a 'tonicity balance' with separate mass balances for water and sodium plus potassium

Useful diagnostic parameters in the differentiation of hyponatremia[54]

Diagnostic parameter	Interpretation
Serum osmolality	
High	Hyperglycemia, glycine solution
Normal	Pseudohyponatremia
Low	Hypotonic hyponatremia
Urine osmolality	
High*	Vasopressin- dependent cause of hyponatremia
Low*	Vasopressin-independent cause of hyponatremia
Urine sodium	
Low	Heart or liver failure, polydipsia, non-renal sodium loss, true volume depletion
High	Diuretics, cerebral and renal salt wasting, SIAD, primary adrenal insufficiency, hypopituitarism
Serum potassium	
Low	Diuretic use, vomiting, diarrhea
High	Primary adrenal insufficiency, renal failure
Serum urea	
Low	SIADH, acute volume expansion
Serum uric acid	
Low	SIADH, renal salt wasting, acute volume expansion
Alkalosis	
Metabolic	Diuretic use, vomiting
Respiratory	Hypopituitarism
Acidosis	
Metabolic	Primary adrenal insufficiency, diarrhea, renal failure

*Compared to serum osmolality

Overview of Hyponatremic Disorders

Pseudohyponatremia

Clinically, pseudohyponatremia can occur during conditions such as hyperlipemic pancreatitis, multiple myeloma, or even hypercholesterolemia. Measuring serum osmolality and arterial serum sodium using a blood gas analyzer (direct potentiometry without sample dilution) are two ways to assess whether pseudohyponatremia is present. Pseudohyponatremia may still occur despite the use of ion-selective electrodes.[58] Two of the three methods for determining the serum sodium concentration (flame photometry and indirect potentiometry) use sample dilution, which can artefactually lower the serum sodium concentration in situations when serum water is displaced by elevated concentrations of lipids or proteins.[42,59]

Hyperglycemia-Induced Hyponatremia

Glucose is an effective osmole, and can therefore attract water from the intracellular to the extracellular compartment. The early recognition of hyperglycemia induced hyponatremia is important because the shift of water is exactly opposite to most of the other hyponatremic disorders. Correction factors exist to assess if the degree of hyperglycemia can explain the degree of hyponatremia, and the ones reported vary between a 1.6 and 2.4-mmol/l fall in natremia for every 5 mmol/l rise in glycemia.[42]

Diuretic-Induced Hyponatremia

Diuretic-induced hyponatremia is probably the most common hyponatremic disorder encountered in clinical medicine, and is mainly associated with the use of

thiazide diuretics. Although the inhibition of the sodium chloride co-transporter by thiazides and the consequent renal sodium loss and volume depletion obviously contribute to hyponatremia, it is not the only factor. This is illustrated by the fact that patients with Gitelman's syndrome, who have an inactivating mutation of the transporter, do not exhibit hyponatremia. Although this may be chronic adaptation, there is also evidence that thiazides may directly stimulate the non-osmotic release of vasopressin. Risk factors for thiazide-induced hyponatremia are age (although not a risk factor according to Sonnenblick et al.[60]) , gender, hypokalemia, and a low lean body mass, while concomitant use of loop diuretics, angiotensin-converting enzyme inhibitors, or nonsteroidal anti-inflammatory drugs were not identified as risk factors.[60,61] Interestingly, Friedman et al.[62] showed that a single dose of a thiazide diuretic may predict the development of hyponatremia because it produced a 5.5-mmol/l fall in serum sodium associated with weight gain in patients with thiazide-induced hyponatremia compared to a 1.2- and 1.8-mmol/l fall in serum sodium and weight loss in healthy controls or elderly hypertensive patients.

Syndrome of Inappropriate Antidiuresis

As discussed in a recent review,[63] the causes of SIAD are myriad, and for the sake of clarity they are best categorized into pulmonary disorders, malignant diseases, disorders of the nervous system, and drug-induced SIAD. Robertson[64] identified four patterns of SIAD including unregulated vasopressin secretion, elevated basal secretion of vasopressin despite normal regulation by osmolarity, a 'reset osmostat' (described in pregnancy, cancer, psychosis, malnourishment, and tuberculosis), and undetectable vasopressin levels, as is found in nephrogenic SIAD.

Nephrogenic SIAD

A conceptually interesting and novel hyponatremic disorder, was recently described in two male children by Feldman et al.[53]; it is caused by an activating mutation of the V2R. The two children presented with the phenotype of classic SIAD (hyponatremia, high urinary sodium and osmolality, normovolemia), but without detectable vasopressin levels. Since this initial discovery, the responsible activating missense mutation R137C has also been identified in pediatric and adult males and females.[65,66] Nephrogenic SIAD should therefore be suspected in any patient with therapy-resistant hyponatremia, undetectable vasopressin levels, unresponsiveness to vasopressin-receptor antagonists and an abnormal response to a water-loading test.[54]

Cerebral Salt Wasting

Cerebral salt wasting is incompletely understood, but the best data on the possible mechanisms come from Berendes et al.[67] who compared patients who had surgery for subarachnoid hemorrhage to patients who had brain tumor surgery. Postoperatively, subarachnoid hemorrhage patients developed polyuria and a natriuresis that correlated with increased B-type natriuretic peptide levels. Throughout the postoperative course, B-type natriuretic peptide was elevated, while aldosterone was suppressed, both contributing to the natriuresis. Vasopressin levels were only briefly elevated, both before and after surgery. Intriguingly, none of the patients developed hyponatremia, which was attributed to tailored saline resuscitation. This emphasizes that hyponatremia is not a prerequisite for the

diagnosis of cerebral salt wasting, but may be more the result of inadequate fluid management.[54]

Hypopituitarism and Primary Adrenal Insufficiency

Hypopituitarism and primary adrenal insufficiency (Addison's disease) are rare but often missed causes of hyponatremia. Hypopituitarism causes hyponatremia primarily because adrenocorticotropin hormone deficiency causes cortisol deficiency which in turn can cause the inappropriate secretion of vasopressin. In primary adrenal deficiency, not only cortisol deficiency but also aldosterone deficiency contribute to hyponatremia, which is why hyperkalemia may also be present. Hypopituitarism can be caused by pituitary or hypothalamic diseases (tumors, trauma, infection, infarction, radiation, surgery). Primary adrenal insufficiency is often caused by autoimmune adrenalitis, but can also be caused by destruction of the adrenal glands by a metastasis or adrenal infections, for example in the acquired immunodeficiency syndrome.[68]

Hyponatremia in Heart and Liver Failure

Heart failure (low cardiac output) or liver failure (systemic vasodilatation) both lead to a low effective arterial blood volume. As a response to the reduced baroreceptor activity, the renin angiotensin system is activated first, whereas the vasopressin axis is activated after a greater decrease in arterial filling. The development of hyponatremia during heart or liver failure is a poor prognostic sign, and hyponatremia has emerged as an independent predictor for mortality.[54] Interestingly, hyponatremia was recently also found to be a predictor of long-term mortality and admission for heart failure after hospital discharge in survivors of

acute ST-elevation myocardial infarction.[69] The explanation for these associations is probably not so much a direct effect of hyponatremia, but rather hyponatremia being a marker for the extent of the so-called 'neurohumoral response', and therefore the degree of decompensation. The central role of hyponatremia in this neurohumoral response has clearly been demonstrated in heart and liver failure, in which hyponatremia correlated with the activity of the renin angiotensin and prostaglandin systems. The neurohumoral response probably also explains why a deterioration of hyponatremia in heart and liver failure coincides with a deterioration in renal function.[54]

Polydipsia and Low Solute Intake

The pathophysiology of the remaining hyponatremic disorders, water polydipsia, beer polydipsia, and hyponatremia due to a low dietary solute intake ('tea and toast'), is independent of vasopressin. Instead, their pathophysiology is explained by polydipsia in combination with solute loss or low solute intake. Thaler et al.[70] demonstrated that electrolyte-free water excretion depends not only on the osmolality and sodium plus potassium content of the urine, but also on the total rate of solute excretion. Therefore, during a low dietary solute intake, solute excretion (mainly urea) can become the rate-limiting step for electrolyte-free water excretion. In this situation, amounts of fluid that are below the water excretory capacity of the kidneys (15–20 liters/day) can cause hyponatremia. Similarly, Musch et al.[71] demonstrated that in hyponatremia due to polydipsia, water intake alone was insufficient to explain the degree of hyponatremia, and that the apparent loss of solutes (possibly through an unknown renal route) played a significant contributory role.

Management

Treatment of hyponatremia must be guided by the patient's clinical presentation, severity of symptoms, estimated duration of illness, fluid status, and underlying etiology for the sodium disturbance. There are 2 groups of hyponatremic patients that will require treatment with either normal saline or hypertonic saline. These 2 groups include patients with: (1) severe but asymptomatic hyponatremia with a sodium level ≤ 110 mEq/L, and (2) acute symptomatic hyponatremia with a sodium level < 120 mEq/L.[40]

Most patients presenting to the ED with hyponatremia are stable and require no emergent therapy; however, asymptomatic patients who have severe hyponatremia with serum sodium levels of ≤ 110 mEq/L and those who have acute alterations in mental status, seizures, or new focal findings due to hyponatremia with serum levels < 120 mEq/L need immediate intervention.[40]

Characteristics of infusates

Infusate	Infusate Na+ (mEqL/L)	Extracellular fluid distribution (%)
3% hypertonic saline	513	100
0.9% NS	154	100
LR	130	97
½ NS	77	73
0.2% NaCl+ D5W	34	55
D5W	0	40

The following equation is helpful to estimate the effect of 1 L of any infusate on serum sodium:[40]

Change in serum Na+ (mEq/L) =

(infusate Na+ (mEq/L) - serum Na+ (mEq/L) / (TBW + 1).

For the past 30 years, the treatment of hyponatremia has remained controversial. In the early 1980s, central pontine myelinolysis, now more accurately labeled as osmotic demyelination syndrome, was described with rapid correction of sodium.[40]

Central nervous system damage due to hyponatremia may be caused by cerebral edema and increased intracranial pressure, by osmotic fluid shifts during overly aggressive treatment, or both. When subjected to a hyponatremic environment, neurons become depleted of sodium and potassium as they attempt to limit their own osmolarity to prevent intracellular fluid shifts that would lead to cerebral edema. If fluid therapy raises extracellular sodium levels too quickly, fluid is pulled out of neurons and diffuse demyelination may occur, leading to flaccid paralysis and, often, death due to this osmotic demyelination syndrome.[72]

While reports of sodium disturbances leading to demyelination syndromes were being published, reports were also being made claiming that severe hyponatremia itself could cause life-threatening brain damage. As of today, the rate at which profound hyponatremia should be corrected is the focus of continued clinical debate. There is no consensus about the optimal treatment of symptomatic hyponatremia. In his well-known 1990 article, Tomas Berl discusses the difficult clinical dilemma that physicians face with patients presenting with symptomatic

hyponatremia because of the different clinical guidelines and lack of true consensus.[73]

There is a very fine line between correcting the sodium too quickly versus too slowly, and inappropriate management can be devastating. Fortunately, over the past few years, we are coming closer to a consensus regarding the optimal treatment of hyponatremia. There is agreement among physicians that correction should occur at a sufficient pace and magnitude to reverse the manifestations of hypotonicity, but not so rapid and large to pose a risk of developing osmotic demyelination. In patients with chronic hyponatremia, neurologic sequelae are more likely to occur with rapid rates of sodium correction.[74,75]

A prospective study looking at neurological outcomes with serial magnetic resonance imaging in hyponatremic patients found that the correction rate of hyponatremia plays a significant role in the pathogenesis of pontine lesions in individuals with profound hyponatremia who undergo large increases in sodium concentration as a result of severe initial hyponatremia.[76]

A comparative multicenter study evaluating 64 patients concluded that patients with severe chronic hyponatremia are most likely to avoid neurologic complications when their electrolyte disturbance is corrected slowly.[77] After weighing the available evidence, Adrogue and Madias recommended a targeted rate of correction that does not exceed 8 mEq/L on any day of treatment.[7] Remaining within this target, the initial rate of correction can be 1 to 2 mEq/L/h for several hours in patients with severe symptoms.[78] In order to minimize the likelihood of osmotic demyelination syndrome, it is essential that symptomatic patients with

severe hyponatremia not have their serum sodium levels rise by any more than a total of 10 to 12 mEq/L within the first 24 hours.[79]

In a multicenter trial of patients with hyponatremia, no neurologic complications were observed in patients corrected by < 12 mEq/L/24h or by < 18 mEq/L/48h.[80] Most cases of osmotic demyelination syndrome occur in the alcoholic, malnourished, and elderly population, although this devastating side effect can occur in healthy, young patients as well. Patients with osmotic demyelination syndrome develop a flaccid paralysis, dysarthria, dysphagia, and hypotension. If a patient develops these symptoms during therapy, stop all sodium-containing fluids and administer D5W immediately to temporarily lower serum sodium levels. Reversal of symptoms has been shown, experimentally, in numerous animal studies and also in 3 human case reports.[81]

For relatively asymptomatic patients with sodium values of 115 to 135 mEq/L, a trial of free water restriction to < 0.8 L/d to 1.25 L/d can be attempted. This includes all fluids, including water contained in food and medications. Serum sodium level should be measured at regular intervals to look for improvement. In more-severe cases, when the sodium is ≤ 120 mEq/L and the patient has either alterations in mental status, focal neurological findings, or seizures, hypertonic saline is indicated.[79,80]

A consensus statement in 2005 suggested that 3% hypertonic saline be used for symptomatic patients, either as a 100 mL (513 mEq of Na+/L) rapid infusion followed by 100 mL/h or at a rate of 1 to 2 mL/ kg/h.30 If a second bolus is required, an additional 100 mL of the 3% solution may be administered over the next 50

minutes. Correction of hyponatremia by 4 to 6 mEq/L within 6 hours, with bolus infusions of 3% saline if necessary, is sufficient to manage the most severe manifestations of hyponatremia.[79]

In a prospective observational study of 58 patients with euvolemic acute symptomatic severe hyponatremia, administration of 100 mL of 3% hypertonic saline resulted in a mean increase in serum sodium of 2 mEq/L.[82]

Studies have also shown that infusing 3% saline at a rate of 1 to 2 mL/kg/h results in an increase in serum sodium of 1 mEq/L/h to 2 mEq/L/h.[63] Potassium deficits must also be replaced aggressively when treating hyponatremic patients. If patients are retaining volume and not diuresing adequately, furosemide can be used. Many authorities recommend concomitant furosemide, although some recommend avoiding it or reserving it for patients with extracellular fluid volume expansion.[78]

Patients may be able to make full neurologic recoveries from osmotic demyelination syndrome with the re-induction of hyponatremia in these extreme cases. In patients with refractory hyponatremia, demeclocycline induces nephrogenic diabetes insipidus and helps to correct hyponatremia in a dosage of 600 to 1200 mg daily.[40,83]

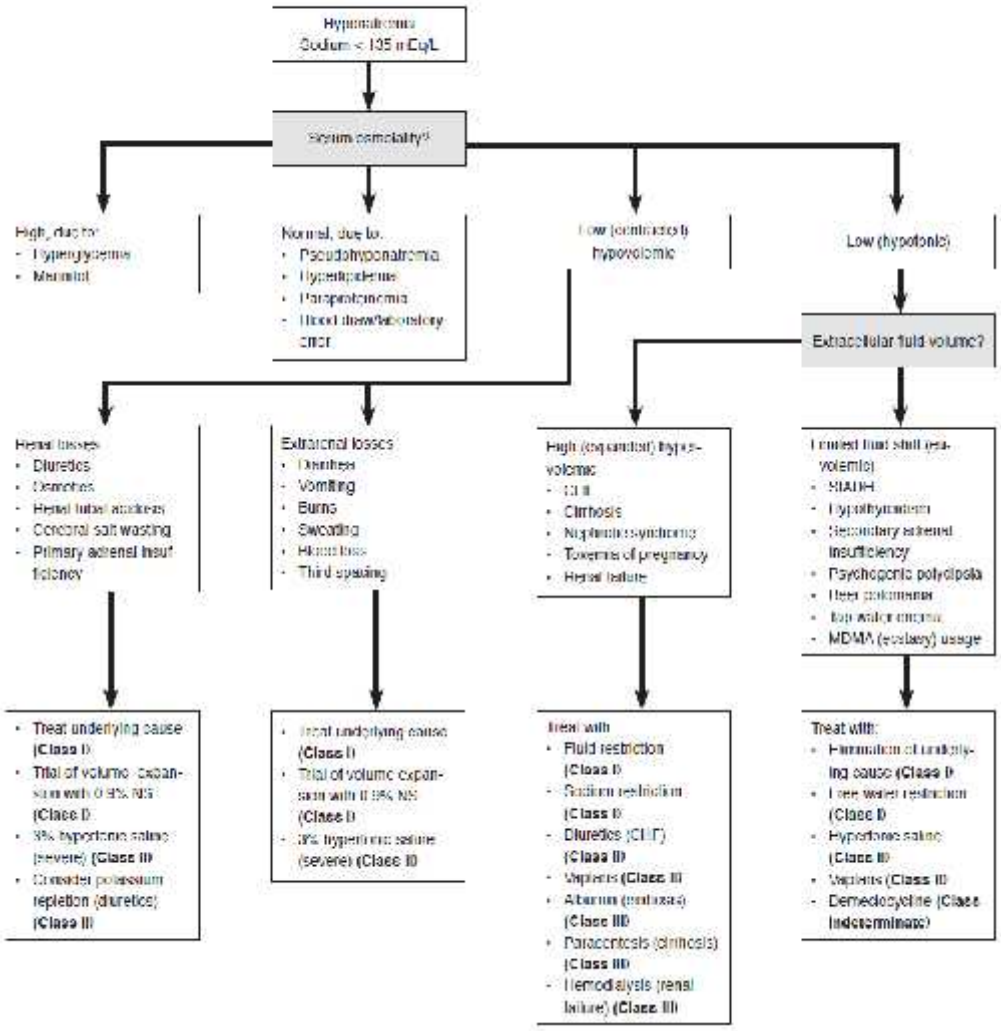


Figure 3. Clinical pathway for the management of hyponatremia in the emergency department[40]

METHODOLOGY

The present study was conducted in the Medical Intensive Care Unit, Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, from January 2014 to December 2014.

Study design

The study design was a one year cross- sectional observational study.

Study period and duration

This study was conducted from January 2014 to December 2014 for a period of one year.

Place

The present study was conducted in the Medical Intensive Care Unit, Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, a teaching hospital attached to Jawaharlal Nehru Medical College, KLE University, Belgaum.

Source of Data

The study comprised of adult patients with moderate to severe hyponatremia admitted to Medical Intensive Care Unit.

Sample size

A total of 100 adult patients with moderate to severe hyponatremia admitted to Medical Intensive Care Unit were selected for the study.

Sampling procedure

The sample size was determined using the following formula as below:

$n = z\alpha^2 * p * q / d^2$

Where, n = Sample size

Zα = Constant which is 1.96 at 95% confidence interval

p = Sensitivity (12) as obtained from previous studies

q = (100-p),

d = Absolute error (8)

Therefore,

$n = 1.96^2 * 12 * 88 / 8^2$

$= 100$

Hence a sample size of 100 was planned.

Selection criteria

Inclusion

- Patients aged ≥ 18 years
- Patients with moderate to severe hyponatremia (Serum sodium ≤ 125 mmol/L)
- Patients admitted to the medical intensive care unit.

Exclusion

- Cases with hyperglycemia, hyperlipidemia and paraproteinemias
- Patients receiving mannitol.

Ethical clearance

Prior to the commencement, ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

The patients fulfilling selection criteria were explained about the nature of the study and a written informed consent was obtained (Annexure I).

Method of collection of data

Patients were interviewed for demographic data such as age and sex. History of other comorbid conditions along with presenting complaints was noted. Further these patients were subjected to a physical examination for clinical signs. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The selected patients underwent the following investigations.

- Complete blood count
- Serum creatinine
- Blood urea nitrogen
- Random blood sugar
- Serum osmolality

- Serum sodium
- Urine sodium
- Urine osmolality

Other investigations like sputum culture, CSF analysis and neuroimaging were done wherever indicated.

Estimation of serum sodium, urine and plasma osmolality and urinary sodium

The sodium estimation was done in the "Easylite" Automated Analyzer by Ion Selective Electrode (ISE) technology. This was followed by a plasma and urinary osmolality determination (osmometer 800 CL) as well as urinary sodium estimation.

Outcome variables

Type of hyponatremia

Based on the investigations the type of hyponatremia was determined as below.

- Euvolemic hypoosmolar
- Hypervolemic hypoosmolar
- Hypervolemic isoosmolar
- Hypovolemic hypoosmolar

Clinical features

The clinical presentation of the study population was assessed and further was evaluated based on type of hyponatremia.

Etiology

Based on the investigations and final diagnosis, the etiology was determined and evaluated in different types of hyponatremia.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and proportions. The continuous data was expressed as mean ± standard deviation (SD). The comparison of categorical data was done using Chi-square test or Fisher's exact test and the comparison of continuous data was done using independent sample 't' test. A probability value ('p' value) of less than or equal to 0.050 at 95% confidence interval was considered as statistically significant.

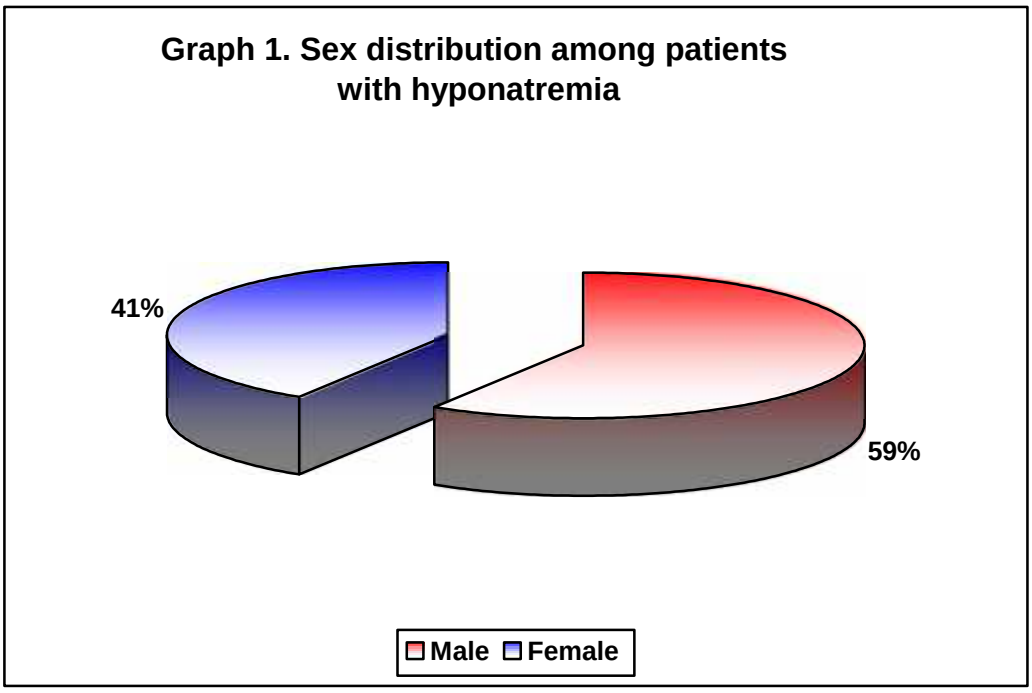
RESULTS

This one year cross sectional observational study was conducted under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 100 patients admitted in the Medical Intensive Care Unit with moderate to severe hyponatremia were included in the study.

The data obtained was analysed and final results were tabulated as below.

Table 1. Sex distribution among patients with hyponatremia

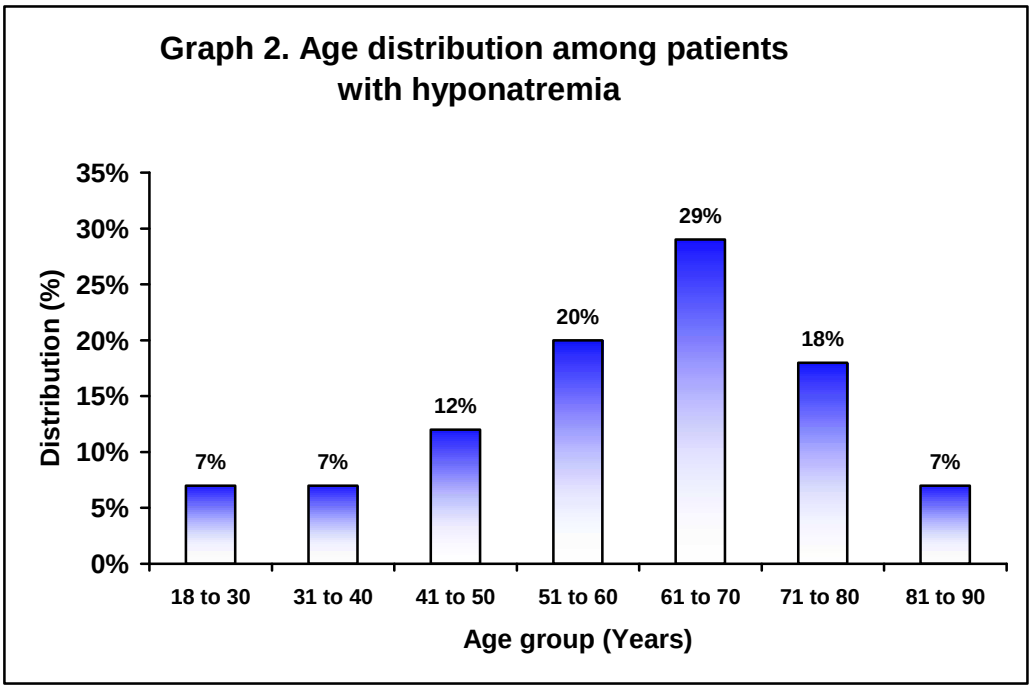
Sex distribution	Distribution (n=100)	
	Number	**Percentage**
Male	59	59.00
Female	41	41.00
Total	**100**	**100.00**



In the present study of 100 patients with hyponatremia, 59% were males and 41% were females. The male to female ratio was 1.43:1.

Table 2. Age distribution among patients with hyponatremia

Age group (Years)	Distribution (n=100)	
	Number	**Percentage**
18 to 30	7	7.00
31 to 40	7	7.00
41 to 50	12	12.00
51 to 60	20	20.00
61 to 70	29	29.00
71 to 80	18	18.00
81 to 90	7	7.00
Total	**100**	**100.00**

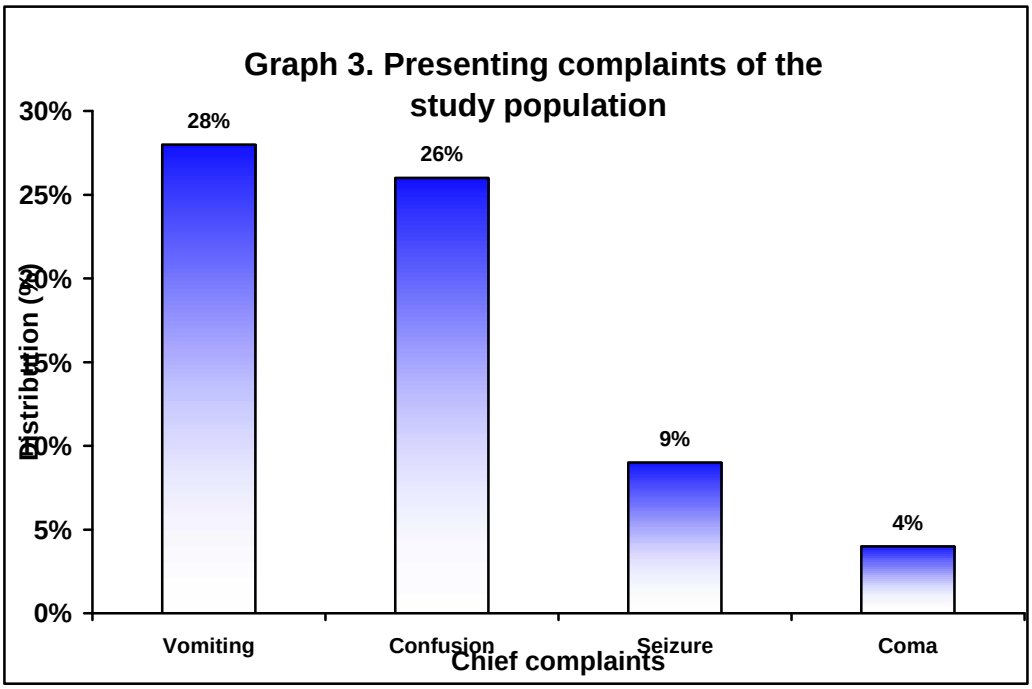


In this study most of the patients were aged between 61 to 70 years (29%).

The mean age of population under study was 58.94 ± 16.10 years.

Table 3. Presenting complaints of the study population

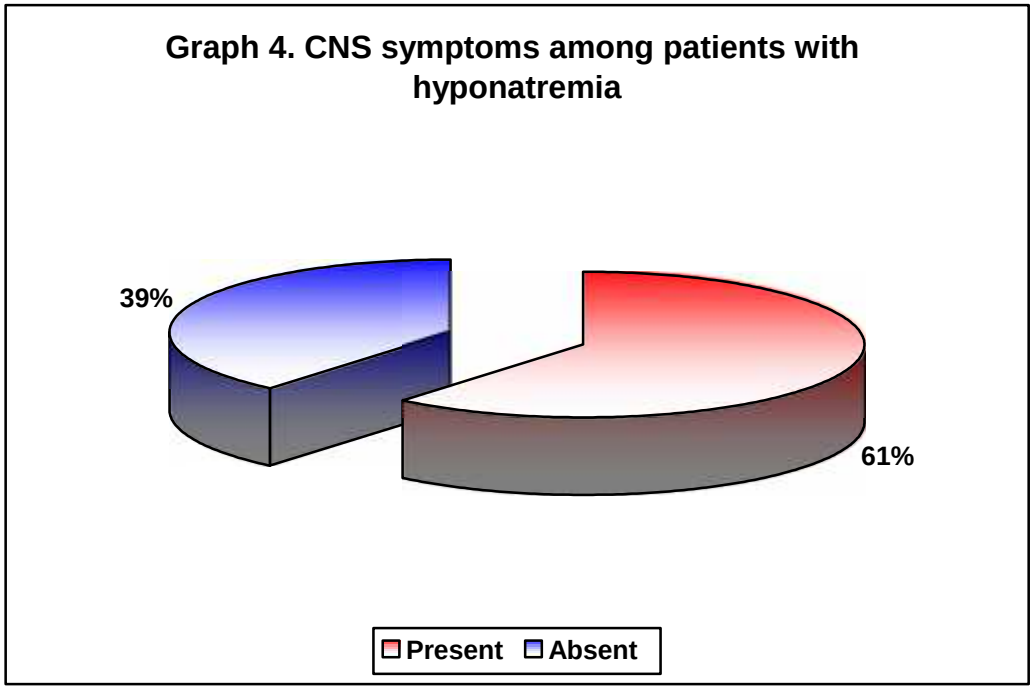
Chief complaints	Distribution (n=100)	
	Number	**Percentage**
Vomiting	28	28.00
Confusion	26	26.00
Seizure	9	9.00
Coma	4	4.00



In the present study commonest presenting complaint was vomiting (28%) followed by confusion (26%), seizure (9%) and coma (4%).

Table 4. CNS symptoms among patients with hyponatremia

CNS Symptoms	Distribution (n=100)	
	Number	Percentage
Present	61	61.00
Absent	39	39.00

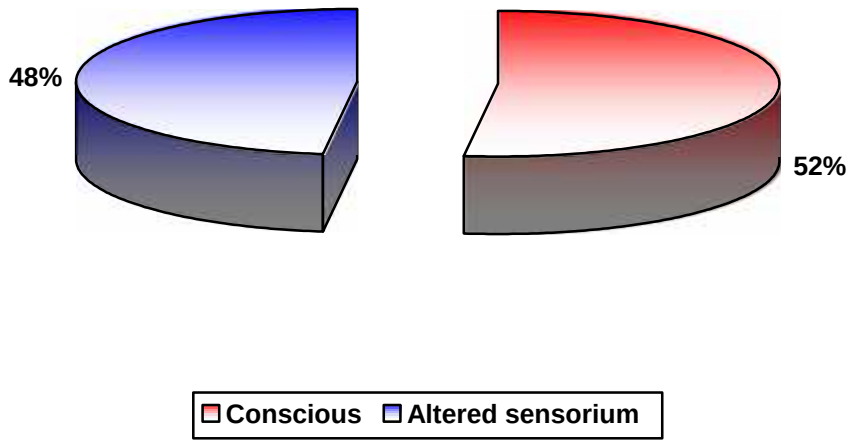


In this study of moderate to severe hyponatremia, CNS symptoms were present among 61% of the patients.

Table 5. Mental status of the study population

Mental status	Distribution (n=100)	
	Number	**Percentage**
Conscious	52	52.00
Altered sensorium	48	48.00
Total	**100**	**100.00**

Graph 5. Mental status of the study population

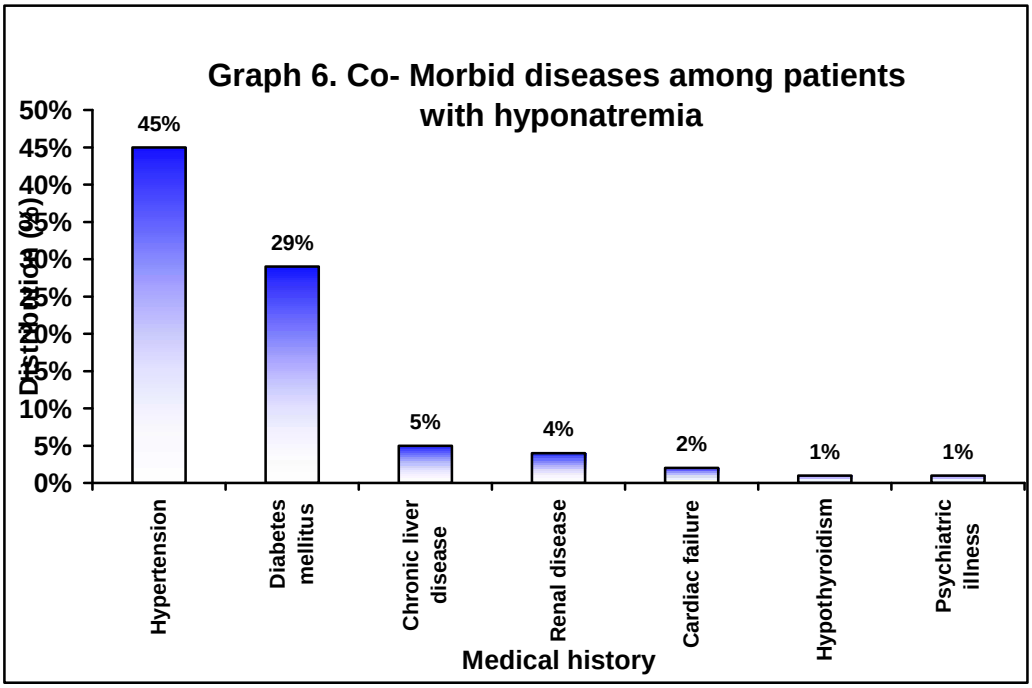


In the present study out of 100 patients 52% of the patients were conscious and 48% of the patients presented with altered sensorium.

Table 6. Co- Morbid diseases among patients with hyponatremia

Medical history	Distribution (n=100)	
	Number	Percentage
Hypertension	45	45.00
Diabetes mellitus	29	29.00
Chronic liver disease	5	5.00
Renal disease	4	4.00
Cardiac failure	2	2.00
Hypothyroidism	1	1.00
Psychiatric illness	1	1.00

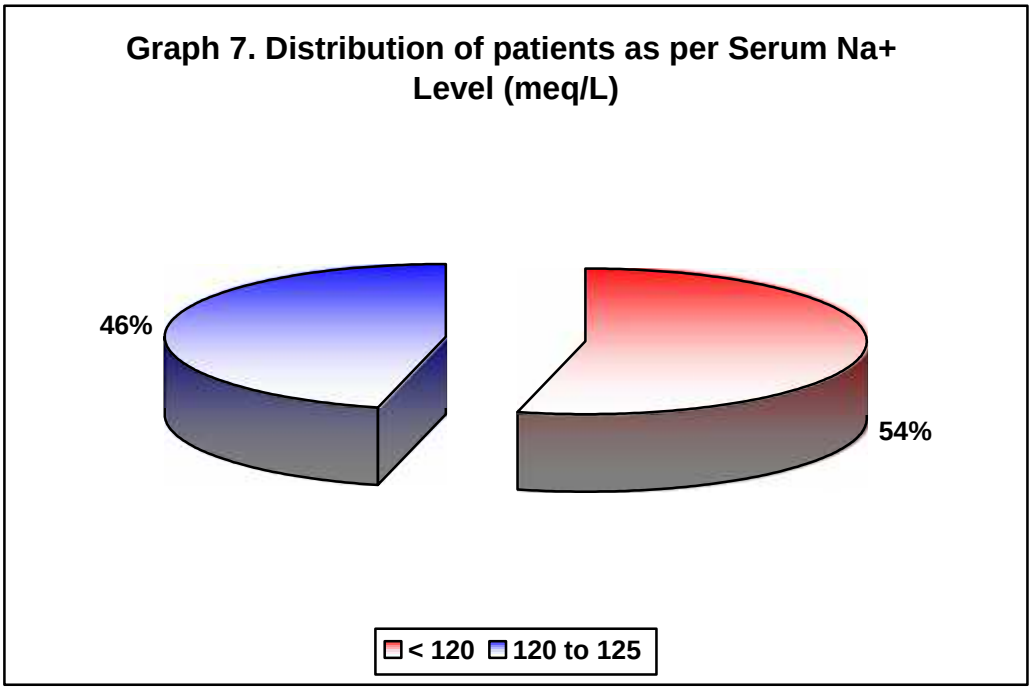
Multiple conditions were present hence total not shown



In this study, comorbid conditions like history of hypertension was present in 49% of the patients and history of diabetes mellitus was noted among 29%.

Table 7. Distribution of patients as per Serum Na^+ Level (meq/L)

Serum sodium	Distribution (n=100)	
	Number	**Percentage**
< 120	54	54.00
120 to 125	46	46.00
Total	**100**	**100.00**

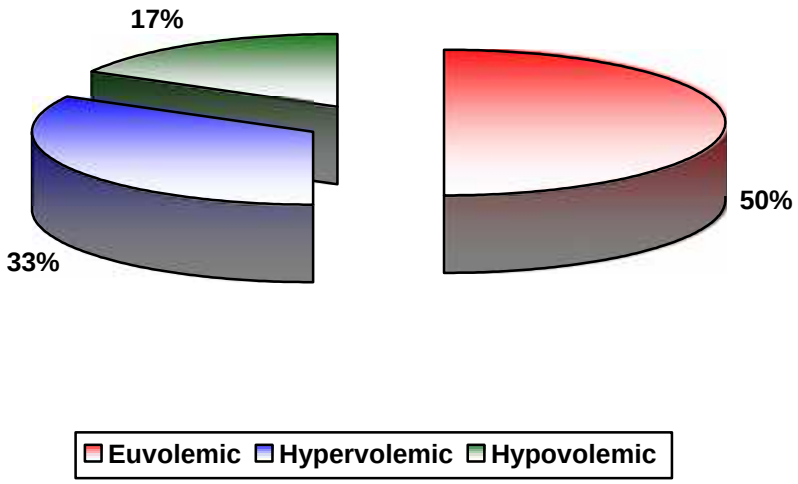


In this study serum sodium levels were < 120 meq/L (severe hyponatremia) in 54% of the patients and 46% of the patients had serum sodium levels between 120 to 125 meq/L (moderate hyponatremia).

Table 8. Hydration status of the study population

Hydration	Distribution (n=100)	
	Number	**Percentage**
Euvolemic	50	50.00
Hypervolemic	33	33.00
Hypovolemic	17	17.00
Total	**100**	**100.00**

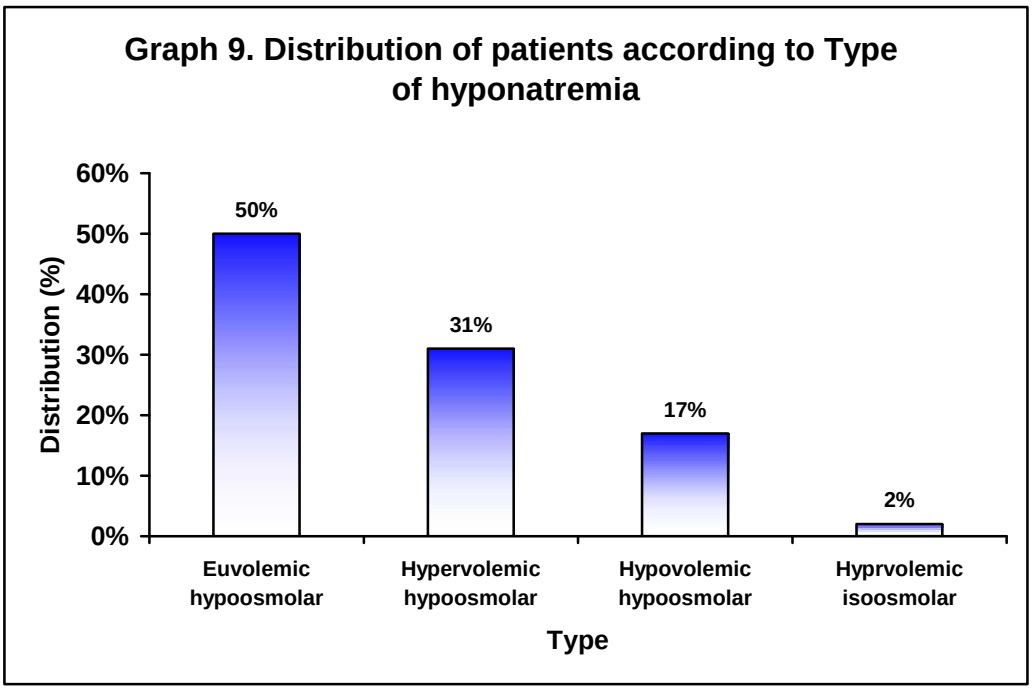
Graph 8. Hydration status of the study population



In the present study on the basis of hydration status, 50% of the patients were euvolemic while 33% and 17% of the patients were hypervolemic and hypovolemic respectively.

Table 9. Distribution of patients according to Type of hyponatremia

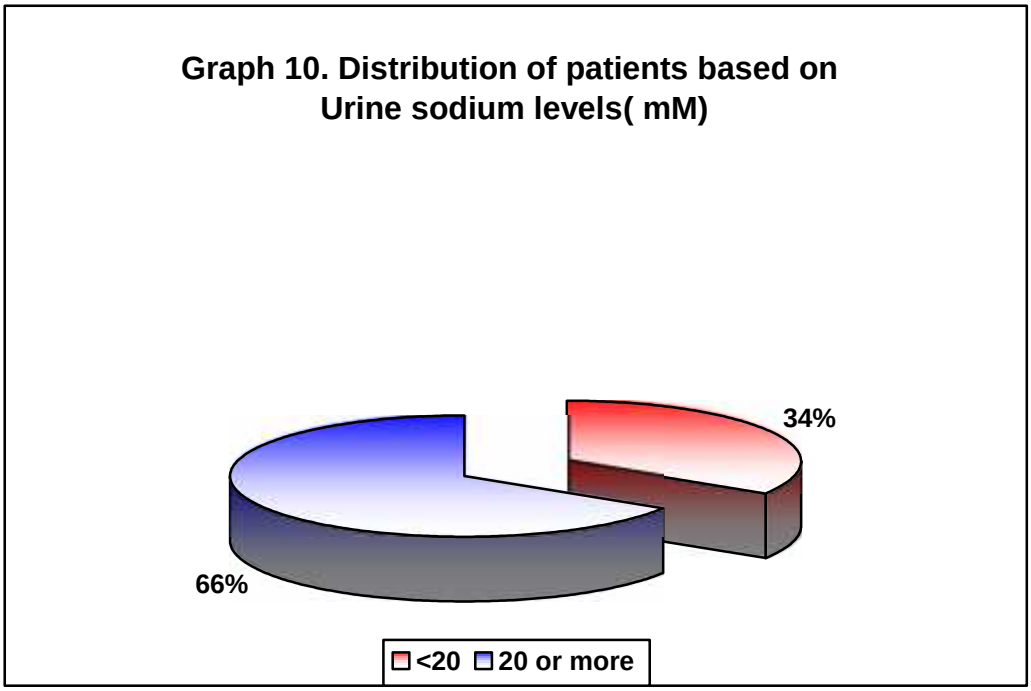
Type	Distribution (n=100)	
	Number	**Percentage**
Euvolemic hypoosmolar	50	50.00
Hypervolemic hypoosmolar	31	31.00
Hypovolemic hypoosmolar	17	17.00
Hypervolemic isoosmolar	2	2.00
Total	**100**	**100.00**



In the present study 50% of the patients had euvolemic hypoosmolar hyponatremia. In the remaining, 31% had hypervolemic hypoosmolar, 17% had hypovolemic hypoosmolar and 2% had hypervolemic isoosmolar hypontaraemia.

Table 10. Distribution of patients based on Urine sodium levels (mM)

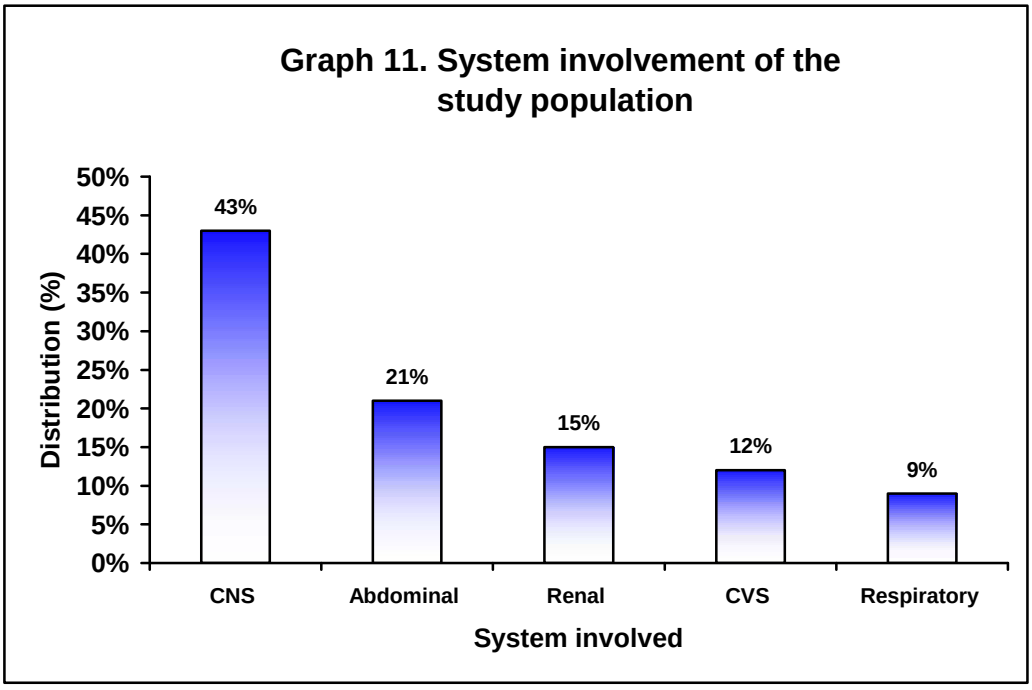
Urine sodium	Distribution (n=100)	
	Number	**Percentage**
20 or more	66	66.00
< 20	34	34.00
Total	**100**	**100.00**



In the present study urine sodium levels were < 20 mM in 34% of the patients and 20 mM or more in 66% of the patients.

Table 11. System involvement of the study population

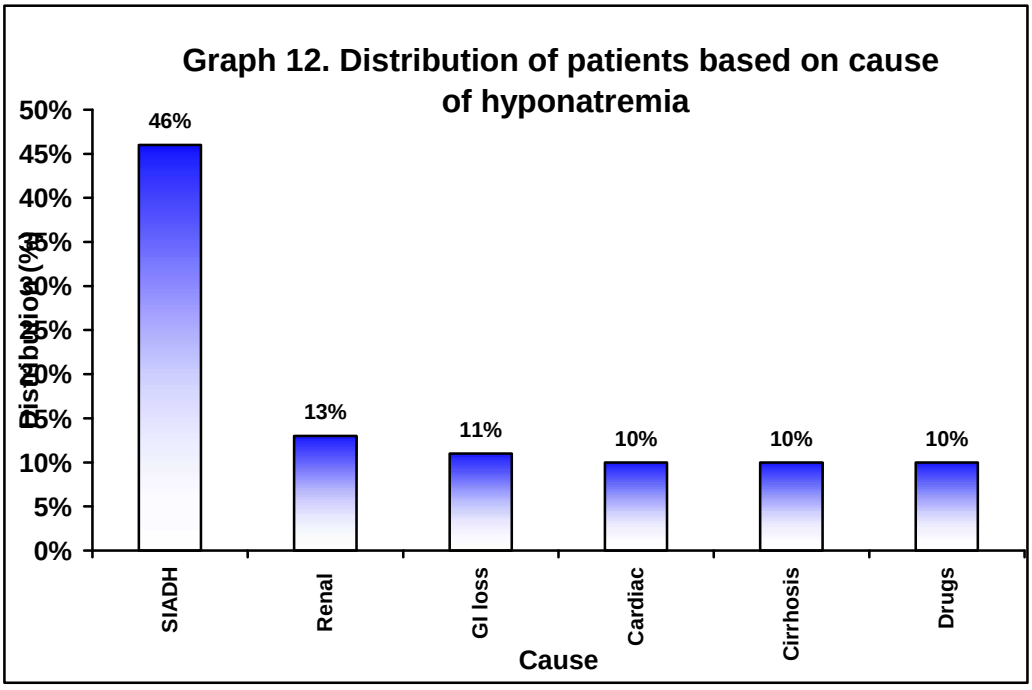
Systems involved	Distribution (n=100)	
	Number	Percentage
CNS	43	43.00
Abdominal	21	21.00
Renal	15	15.00
CVS	12	12.00
Respiratory	9	9.00



In this study, among patients with hyponatremia, central nervous system involvement was noted in 43% of the patients. The involvement of other systems is as shown in table 11 and graph 11.

Table 12. Distribution of patients based on cause of hyponatremia

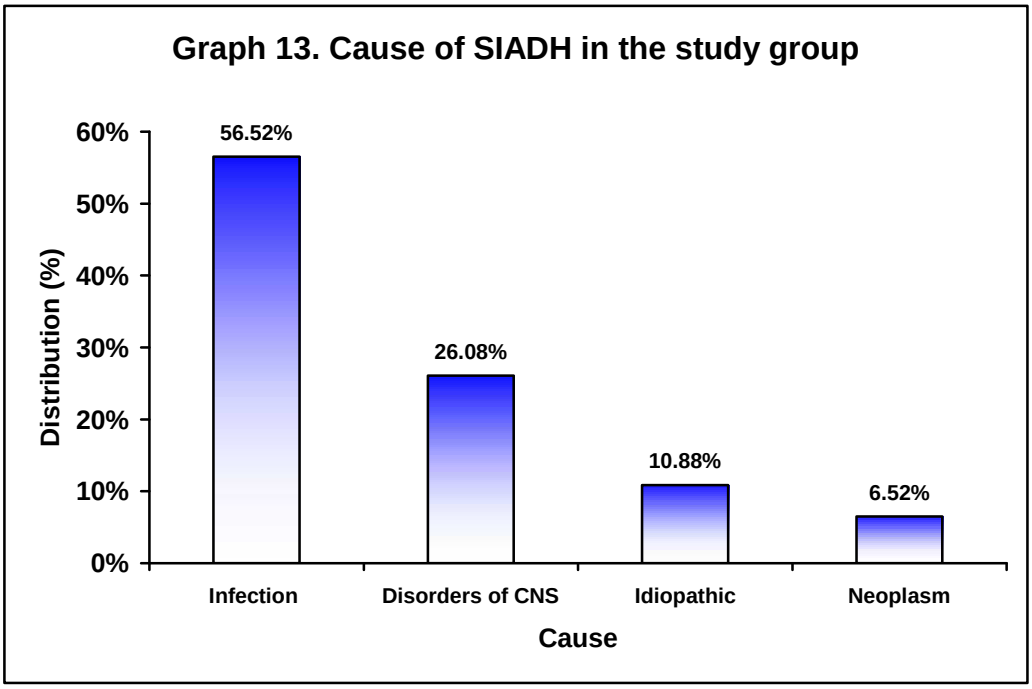
Cause	Distribution (n=100)	
	Number	**Percentage**
SIADH	46	46.00
Renal	13	13.00
GI loss	11	11.00
Cirrhosis	10	10.00
Drugs	10	10.00
Cardiac	10	10.00
Total	**100**	**100.00**



In the present study SIADH was the commonest cause of hypontraemia noted among 46% of the patients. The other causes are as depicted in table 12.

Table 13. Cause of SIADH in the study group

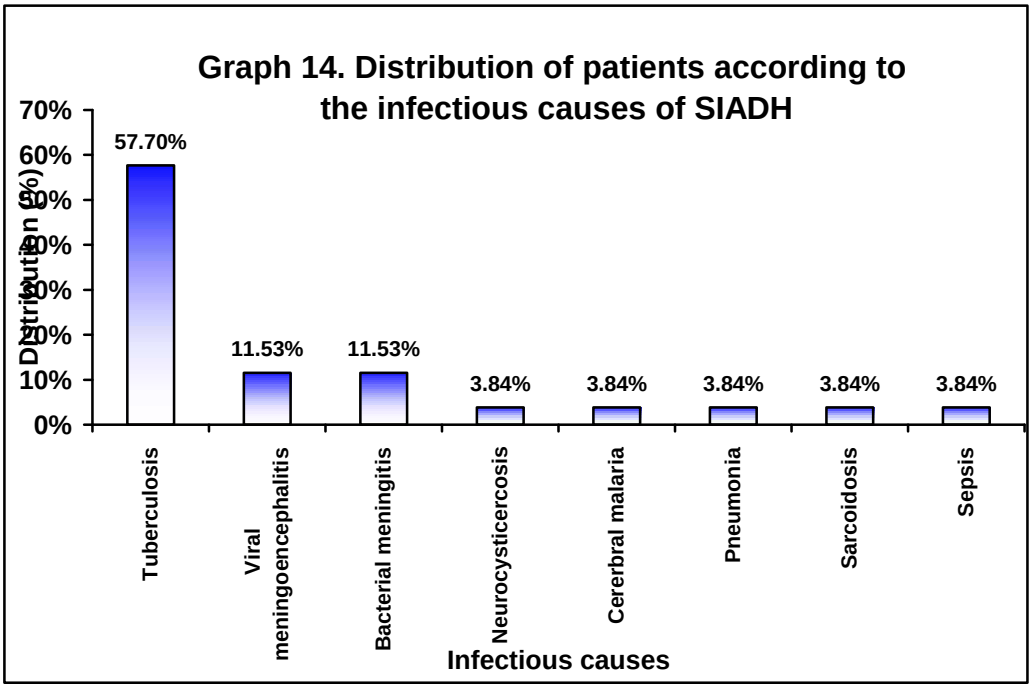
Cause	Distribution (n=46)	
	Number	**Percentage**
Infection	26	56.52
Disorders of CNS	12	26.08
Idiopathic	5	10.88
Neoplasm	3	6.52
Total	**46**	**100.00**



In the present study, Infections (56.52%) were the predominant cause of SIADH followed by disorders of CNS (26.08%).

Table 14. Distribution of patients according to the infectious causes of SIADH

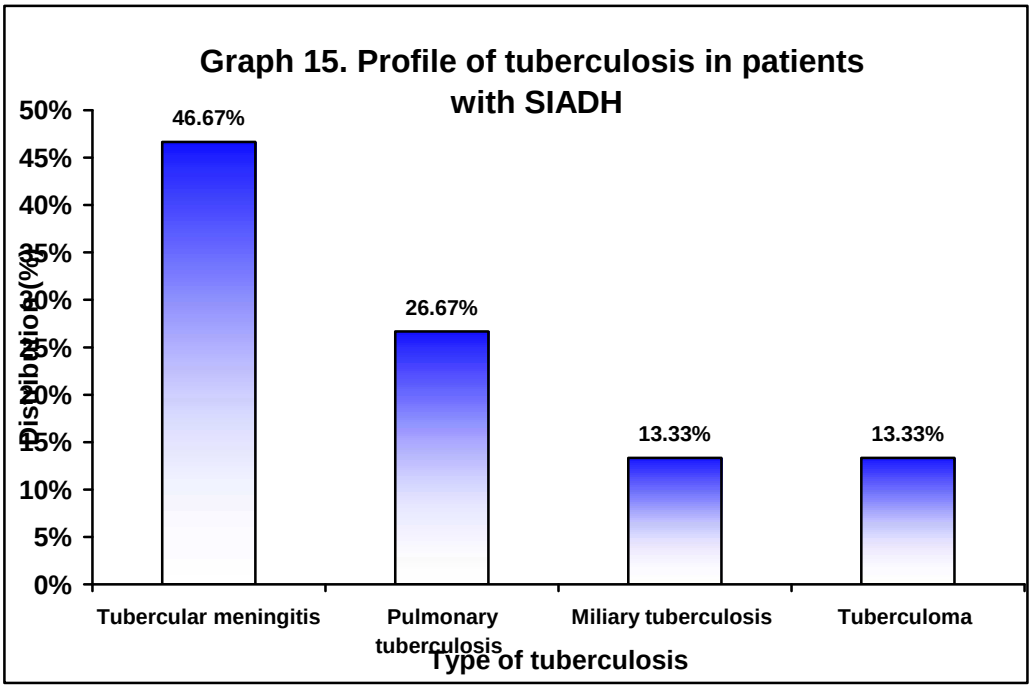
Cause	Distribution (n=26)	
	Number	**Percentage**
Tuberculosis	15	57.70
Viral meningoencephalitis	3	11.53
Bacterial meningitis	3	11.53
Neurocysticercosis	1	3.84
Cerebral malaria	1	3.84
Pneumonia	1	3.84
Sarcoidosis	1	3.84
Sepsis	1	3.84
Total	**26**	**100.00**



In the present study the commonest infectious etiology of SIADH was tuberculosis (57.7%) followed by viral meningoencephalitis and bacterial meningitis (11.53% each).

Table 15. Profile of tuberculosis in patients with SIADH

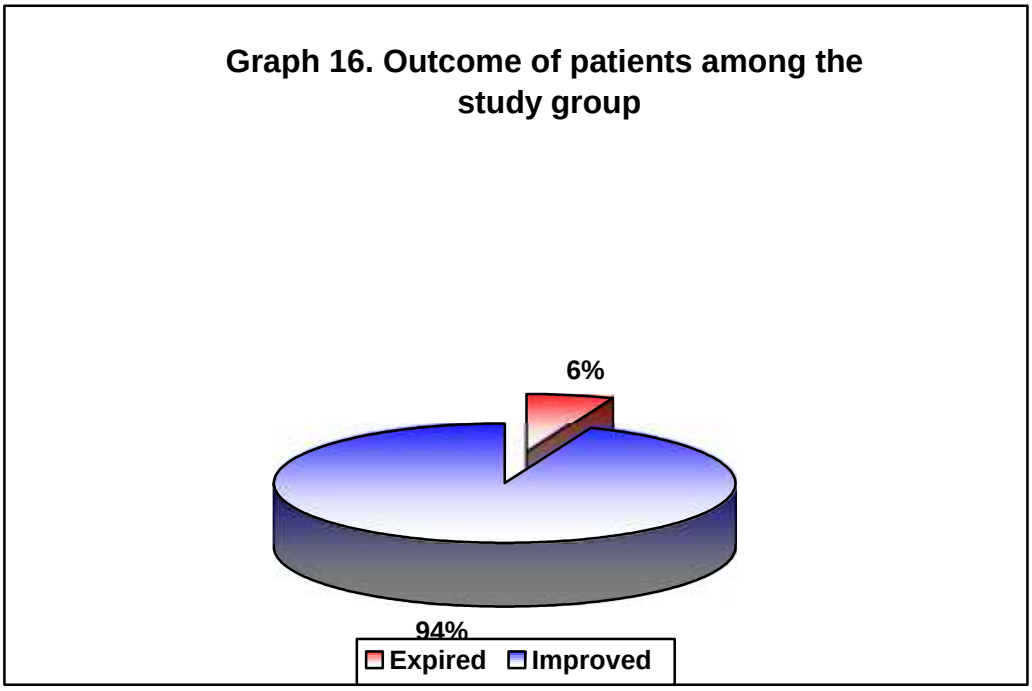
Type of Tuberculosis	Distribution (n=15)	
	Number	**Percentage**
Tubercular meningitis	7	46.67
Pulmonary tuberculosis	4	26.67
Miliary tuberculosis	2	13.33
Tuberculoma	2	13.33
Total	**15**	**100.00**



In the present study most common form of tuberculosis among patients of SIADH was tubercular meningitis (46.67%).

Table 16. Outcome of patients among the study group

Outcome	Distribution (n=100)	
	Number	**Percentage**
Improved	94	94.00
Expired	6	6.00
Total	**100**	**100.00**



In the present study majority (94%) of the patients improved and mortality was noted in 6% of the patients.

Table 17. Association of sex with severity of hyponatremia

Sex	Hyponatremia				Total	
	Severe (<120)		Moderate (120-125)			
	No	**%**	**No**	**%**	**No**	**%**
Male	33	55.93	26	44.07	59	100.00
Female	21	51.22	20	48.78	41	100.00
Total	**54**	**54.00**	**46**	**46.00**	**100**	**100.00**

p = 0.642

In the present study no association was found between sex and severity of hyponatremia (p=0.642).

Table 18. Association of age with severity of hyponatremia

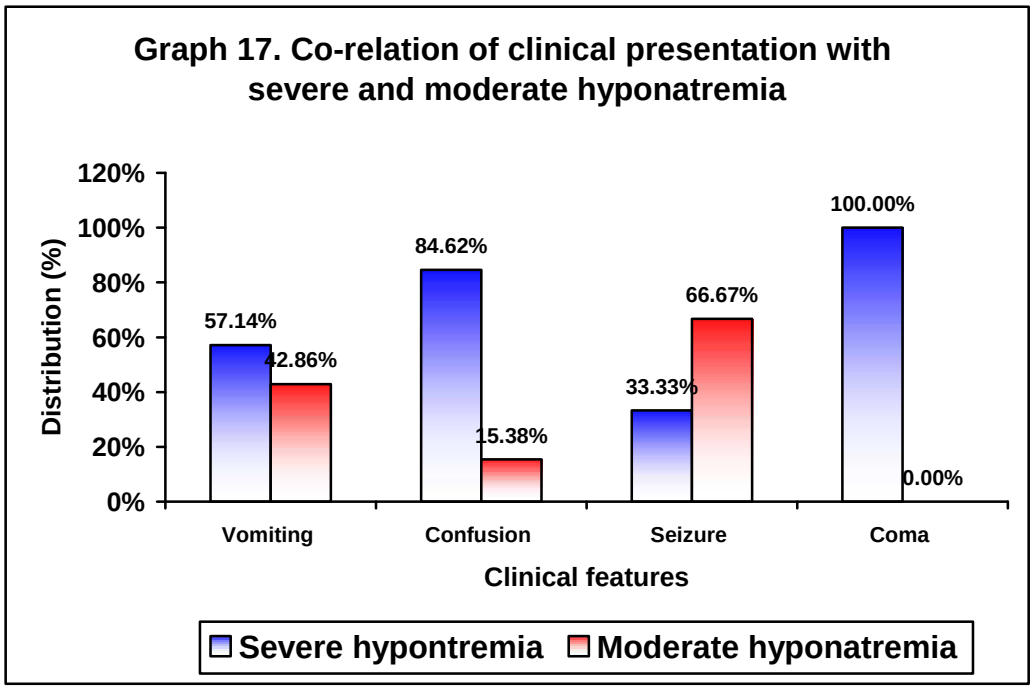
Age group (Years)	Hyponatremia				Total	
	Severe (<120)		Moderate (120-125)			
	No	**%**	**No**	**%**	**No**	**%**
18 to 30	3	42.86	4	57.14	7	100.00
31 to 40	5	71.43	2	28.57	7	100.00
41 to 50	7	58.33	5	41.67	12	100.00
51 to 60	7	35.00	13	65.00	20	100.00
61 to 70	15	51.72	14	48.28	29	100.00
71 to 80	10	55.56	8	44.44	18	100.00
81 to 90	7	100.00	0	0.00	7	100.00
Total	**54**	**54.00**	**46**	**46.00**	**100**	**100.00**

p = 0.098

In this study the severity of hyponatremia was comparable in all the age groups (p=0.098).

Table 19. Co-relation of clinical presentation with severe and moderate hyponatremia

Clinical presentation	Findings	Hyponatremia						p value
		Severe (<120)		Moderate (120-125)		Total		
		No	%	No	%	No	%	
Vomiting	Yes	16	57.14	12	42.86	28	100.00	0.824
	No	38	52.78	34	47.22	72	100.00	
	Total	**54**	**54.00**	**46**	**46.00**	**100**	**100.00**	
Confusion	Yes	22	84.62	4	15.38	26	100.00	**<0.001**
	No	32	43.24	42	56.76	74	100.00	
	Total	**54**	**54.00**	**46**	**46.00**	**100**	**100.00**	
Seizure	Yes	3	33.33	6	66.67	9	100.00	0.170
	No	51	56.04	40	43.96	91	100.00	
	Total	3	33.33	6	66.67	9	100.00	
Coma	Yes	4	100.00	0	0.00	4	100.00	**0.081**
	No	50	52.08	46	47.92	96	100.00	
	Total	**54**	**54.00**	**46**	**46.00**	**100**	**100.00**	



In this study, confusion was significantly high in patients with severe hyponatremia as compared to moderate hyponatremia (84.62 vs 15.38%; p<0.001).

Table 20. Association of causes with type of hyponatremia

Causes	Type of hyponatremia								Total	
	Euvolemic hypoosmolar		Hypervolemic hypoosmolar		Hypervolemic isoosmolar		Hypovolemic hypoosmolar			
	No	%	No	%	No	%	No	%	No	%
Cardiac	0	0.00	10	100.00	0	0.00	0	0.00	10	100.00
Cirrhosis	0	0.00	10	100.00	0	0.00	0	0.00	10	100.00
Drugs	4	40.00	0	0.00	0	0.00	6	60.00	10	100.00
GI loss	0	0.00	0	0.00	0	0.00	11	100.00	11	100.00
Renal	0	0.00	10	76.92	2	15.38	1	7.69	13	100.00
SIADH	46	100.00	0	0.00	0	0.00	0	0.00	46	100.00
Total	**50**	**50.00**	**30**	**30.00**	**2**	**2.00**	**18**	**18.00**	**100**	**100.00**

p<0.001

In the present study most of the patients had SIADH as cause of hyponatremia and all these patients had euvolemic hypoosmolar hypontraemia. Similarly all the patients with cardiac and cirrhosis causes had hypervolemic hypoosmolar hyponatremia and this difference was statistically significant (p<0.001).

Table 21. Association of causes with severe and moderate hyponatremia

Causes	Hyponatremia				Total	
	Severe (<120)		Moderate (120-125)			
	No	%	No	%	No	%
Cardiac	5	50.00	5	50.00	10	100.00
Cirrhosis	3	30.00	7	70.00	10	100.00
Drugs	7	70.00	3	30.00	10	100.00
GI loss	8	72.73	3	27.27	11	100.00
Renal	9	69.23	4	30.77	13	100.00
SIADH	22	47.83	24	52.17	46	100.00
Total	**54**	**54.00**	**46**	**46.00**	**100**	**100.00**

p = 0.248

In this study no association was found between severity and causes of hyponatremia (p=0.328).

Table 22. Association of mental status with severity of hyponatremia

Mental status	Hyponatremia				Total	
	Severe (<120)		Moderate (120-125)			
	No	%	No	%	No	%
Conscious	24	46.15	28	53.85	52	100.00
Altered sensorium	30	62.50	18	37.50	48	100.00
Total	**54**	**54.00**	**46**	**46.00**	**100**	**100.00**

In this study 48 patients had altered sensorium of which 30 (62.5%) had severe and 18 (38.5%) patients had moderate hyponatremia.

Table 23. Association of causes with urine sodium

Causes	Urine sodium (in mM)				Total	
	<20		20 or more			
	No	%	No	%	No	%
Cardiac	10	100.00	0	0.00	10	100.00
Cirrhosis	10	100.00	0	0.00	10	100.00
Drugs	2	20.00	8	80.00	10	100.00
GI loss	11	100.00	0	0.00	11	100.00
Renal	1	7.69	12	92.31	13	100.00
SIADH	0	0.00	46	100.00	46	100.00
Total	**34**	**34.00**	**66**	**66.00**	**100**	**100.00**

p<0.001

In this study significantly higher number of the patients had high urine sodium (25 mM or more) among the patients with SIADH (100%) and renal causes (92.31%) (p<0.001).

DISCUSSION

Despite being the commonest electrolyte imbalance, hyponatremia remains incompletely understood in many basic areas. Its association with a plethora of underlying disease states, and its multiple etiologies with differing pathophysiological mechanisms makes diagnosis challenging. Moderate to severe hyponatremia is known to increase inpatient mortality and therefore, this study was undertaken as an attempt to describe the clinical profile and to find out etiology among patients with moderate to severe hyponatremia in the Medical intensive care unit settings.[84]

This one year cross sectional observational study was carried out among 100 patients who presented with moderate to severe hyponatremia. The patients who satisfied the selection criteria and were admitted in Medical Intensive Care Unit under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014 were enrolled.

In our study of 100 patients admitted with moderate to severe hyponatremia slight male preponderance was noted with 59% of patients being male. The male to female ratio was 1.43:1. Similar sex distribution pattern was reported by Rahil AI et al.[84] where 33 (62.3%) patients with hyponatremia were males and 20 (37.7%) were females. In the present study unlike many other studies no association was found between sex and severity of hyponatremia (p=0.642).

The incidence of hyponatremia is higher in the elderly. This group is more vulnerable mainly owing to impaired ability to maintain water and electrolyte

homeostasis in response to dietary and environmental changes. In similarity to other reports[85-87] hyponatremia in our study was more prevalent among elderly patients than in younger patients (54 % vs. 44 %). Most of the patients were aged between 61 to 70 years (29%) followed by 51 to 60 years (20%), 71 to 80 years (18%) and 41 to 50 years (12%). However, more than half of the study population (54%) had age ≥ 60 years and the mean age was 58.94 ± 16.10 years. These findings were consistent with a study by Rahil AI et al.[84] who reported mean age as 56± 20 years (range of 17-93 years).

The clinical presentations of hyponatremia can range from mild non specific symptoms such as nausea, headache, and lethargy, to severe symptoms like seizures and coma.[88] In our study commonest symptom reported was vomiting which was present in 28% of the patients. A significant number of patients had confusion (26%) as a presenting complaint. The other presentations included seizures (9%) and coma (4%). In a study by Manish Patni et al.[89] from Nagpur, Maharashtra, similar findings were reported with drowsiness as the commonest symptom present in 51% of the cases, 14% of patients had vomiting while 6% patients had seizures. In our study when symptoms were co related with severity of hyponatremia, confusion was significantly high in patients with severe hyponatremia as compared to moderate hyponatremia. (84.62 vs 15.38%; $p<0.001$).

In our study, more than half the study population presented with CNS symptoms (61%). Recently, a descriptive study by Rao MY. et al.[90] from Bangalore, Karnataka reported 76% of patients with CNS symptoms which was similar to our study. A study by Rahil AI et al,[84] showed CNS involvement in 24.5% of the patients with symptoms that ranged from confusion to coma. Similarly, in our study,

48 patients had altered sensorium of which 30 (62.5%) patients had severe and 18 (38.5%) patients had moderate hyponatremia. Also, some of the patients in our study presented with other non-CNS symptoms such as pain in abdomen, lethargy and decreased appetite.

In the present study nearly half of the study population had history of hypertension (49%) and nearly one third had history of diabetes mellitus (29%). Similar findings were reported in a study by Rao MY. et al.[90] from Bangalore, Karnataka where most of the patients had multiple co-morbid conditions of which hypertension and diabetes were the most common. Hyponatremic hypertensive syndrome is a well-known entity, the most common association being in patients with essential hypertension receiving diuretics[91] which are known to interfere with metabolism of various electrolytes and predispose them to electrolyte imbalance. Along with their effect on sodium-chloride co-transporter channel, thiazide diuretics are known to cause non-osmotic release of vasopressin.[90]

In the present study out of 100 patients studied, serum sodium levels were < 120 meq/L in 54% of the patients whereas 46% had serum sodium levels between 120 to 125 meq/L, thus, confirming moderate hyponatremia in 54% and severe among 46% of the patients. These findings were consistent with a study by Rahil AI et al.[84] which describes the clinical presentation and etiology of moderate and severe hyponatremia in patients admitted to Hamad general hospital in Doha. The authors reported 53 patients with moderate to severe hyponatremia from June 2007 to July 2008. Of all, 31 (58.4%) patients had moderate hyponatremia, whereas 22 (41.6%) patients had severe hyponatremia. Recently another study by Chowdhary R. et al.[92] from Intensive care unit of SSKM Hospital / IPGME&R, Kolkata during April 2011

to March 2012 among 70 patients reported mild hyponatremia in 27.14% of the patients and moderate in 37.14% of the patients while severe hyponatremia was noted among 35.72% of the patients.

The central nervous system is the commonest involved system, observed in the present study as well as other studies. Headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. These symptoms are more conspicuous when the decrease in the serum sodium concentration is large or rapid (i.e., occurring within a period of hours). Complications of severe and rapidly evolving hyponatremia include seizures, coma, permanent brain damage, respiratory arrest, brain-stem herniation and death.[93]

In the present study the hydration status in half of the study population (50%) was euvolemic while one third (33%) were hypervolemic and hypovolemia was noted among 17% of the patients. Further based on osmolality most of the patients (50%) had euvolemic hypoosmolar hyponatremia followed by hypervolemic hypoosmolar hyponatremia (31%), hypovolemic hypoosmolar hyponatremia was seen in 17% and hypervolemic isoosmolar hyponatremia in 2% of patients. Similar pattern was reported in a study by Rao MY et al.[90] where 61% were euvolemic, 23% were overloaded and 16% dehydrated and the commonest type of hyponatremia noted was isovolemic hypo-osmolar hyponatremia.

Hypotonic hyponatremia causes entry of water into the brain, resulting in cerebral edema. Because the surrounding cranium limits expansion of the brain, intracranial hypertension develops, with a risk of brain injury. Fortunately, solutes leave brain tissues within hours, thereby inducing water loss and ameliorating brain

swelling. This process of adaptation by the brain accounts for the relatively asymptomatic nature of even severe hyponatremia if it develops slowly. Nevertheless, this brain adaptation is also the source of risk of osmotic demyelination. Although rare, osmotic demyelination is serious and can develop one to several days after aggressive treatment of hyponatremia by any method, including water restriction alone. Shrinkage of the brain triggers demyelination of pontine and extrapontine neurons that can cause neurologic dysfunction, including quadriplegia, pseudo bulbar palsy, seizures, coma, and even death. Hepatic failure, potassium depletion, and malnutrition increase the risk of these complications.[25]

Distinguishing the cause(s) of hyponatremia may be challenging in clinical practice. Hyponatremia is ascribed to either water retention or (less often) loss of effective solute (sodium plus potassium) in excess of water. Because the capacity for water excretion normally is so great, the retention of water resulting in hyponatremia takes place only in the presence of conditions that impair renal excretion of water. An exception to this rule is primary polydipsia, in which the excessive water intake can overwhelm even normal excretory capacity. Given that suppression of arginine vasopressin (antidiuretic hormone [ADH]) secretion is essential for the excretion of any water load, the presence of high serum ADH concentrations is the sine qua non for the development and maintenance of hyponatremia.[84]

Virtually, all causes of hyponatremia (except renal failure and primary polydipsia) are characterized by an excess of ADH (despite the presence of hypotonicity), which is most frequently caused by the syndrome of inappropriate ADH secretion (SIADH) or depletion of effective circulating volume (which is a normal stimulus to ADH secretion).[52,94] In spite of being the most usual etiological

factor for hyponatremia in hospitalized elderly patients[25] as well as the most common cause of normovolemic hyponatremia, the syndrome of inappropriate ADH secretion (SIADH) is normally diagnosed by exclusion of other causes including diuretics and renal, liver, thyroid, adrenal, and pituitary diseases.[95]

Similarly in the present study also SIADH was the commonest cause of hyponatremia noted in nearly half of the study population (46%). The other causes were renal loss (13%), gastrointestinal loss (11%) while cirrhosis of liver, drugs induced and cardiac causes constitute 10% each. In a prospective study conducted in a general medical-surgical setting,[52] 66 patients (34%) had euvolemic hyponatremia, 38 (19%) had hypervolemic hyponatremia associated with edematous disorders, and 33 (17%) had hypovolemic conditions, chiefly related to gastro intestinal fluid loss or diuretic use. In a study by Rahil AI et al.[84] extra-renal fluid loss including vomiting, diarrhea, or diaphoresis were the most frequent cause of hyponatremia which was found in 33.9% of the patients. SIADH was considered to be the cause in 20.7% of the patients. Diuretics (mainly thiazide) were found to be the cause of hyponatremia in 18.9% of the patients. Nearly half the patients with severe hyponatremia had SIADH in the study done by Clayton et al.[96] Laczi reported that SIADH was the most common cause of euvolemic hyponatremia in their study in Hungary.[97] Another study by Paniker GI et al.[93] on clinical profile of hyponatremia in ICU hospitalized patients also reported SIADH as a predominant cause for hyponatremia.

In our study we tried searching for the cause of SIADH among patients having hyponatremia, as treating the cause would prevent considerable morbidity and mortality associated with this disorder. In the present study, infections (56.52%)

were the predominant cause of SIADH followed by disorders of CNS (26.08%). These disorders of CNS included cerebrovascular accidents and Guillain-Barre syndrome. There were 3 patients (6.52%) with Neoplasm as the cause of SIADH while in 5 patients (10.8%) no cause could be found and were thus classified as idiopathic.

Since infections formed the major chunk of the patients of SIADH, we went ahead and further classified the patients, based on the site and type of infection. An alarming 57.7% of patients having an infectious etiology as the cause of SIADH had tuberculosis, 46% of them had tubercular meningitis, 26% had pulmonary tuberculosis, while 13 % had miliary tuberculosis and tuberculomas each. Other infections included viral meningoencephalitis and bacterial meningitis (11% each)

In 1969, Chung and Hubbard[98] reported that 11% of patients with active TB (pulmonary or non-pulmonary) are affected with hyponatremia, and it is apparent that the main cause of serum sodium depletion in these patients is SIADH. Vorherr et al.[99] have reported a case with Pulmonary TB and hyponatremia and found antidiuretic agents in tuberculous lung tissues. Bryant et al.[100] has suggested the syndrome of inappropriate secretion of antidiuretic hormone for patients with an infectious pulmonary disease such as Pulmonary TB. Cockcroft et al.,[101] reported a 74-year-old woman with miliary tuberculosis which was complicated by severe hyponatremia due to SIADH. In one of the first reports, Weiss et al.,[102] reported hyponatremia resulting from SIADH in patients with Pulmonary TB. Then it was declared that an increased ADH level in the presence of hyponatremia in Pulmonary TB cases is an indicator for ectopic ADH production. Few studies demonstrated that the ADH level was not detectable following full anti-TB therapy.[103,104] There are

many reports of SIADH associated with pulmonary, miliary and central nervous system-related TB. More than 60% of the patients with tubercular meningitis may present with hyponatremia or SIADH as the first presentation.[105] Multiple infectious diseases are associated with this syndrome.[106]

Endocrine system involvements by TB, as the other mechanism, can also induce hyponatremia which is important to consider in patients with pulmonary TB. Tuberculosis was revealed to involve adrenal glands directly and this involvement lead to overt or subclinical adrenal insufficiency and hyponatremia. Pituitary gland may also be involved by the tuberculosis bacilli. Hypopituitarism has been reported in 20% of cases years after the treatment of tubercular meningitis in childhood. The reason seemed to be tuberculosis lesions impressing the hypothalamus, pituitary stalk and indirectly or directly, the pituitary gland itself.[107]

SIADH is commonly reversible with effective Pulmonary TB treatment in most cases. Therefore, it should be carefully looked for by the treating physician as a cause of hyponatremia. Also, patients who were affected by hyponatremia were more likely to have higher mortality as suggested in a study by Sharma et al.[108]

In the present study majority (94%) of the patients improved and mortality was noted in only 6% of the patients, this finding is consistent with another study by Joseph and Paniker where mortality was noted in 7% of patients.[93]

CONCLUSION

Based on the findings of this study it may be concluded that, hyponatremia can present with protean clinical manifestations. The presentation can vary from mild symptoms such as vomiting, lethargy, malaise to severe forms such as confusion, seizure and coma. Majority of patients report CNS symptoms and these patients are likely to have euvolemic hypoosmolar hyponatremia with SIADH as the predominant cause. Confusion usually is the most common presenting complaint of severe hyponatremia. The severity of hyponatremia is independent of age, sex and type of hyponatremia, as it is the rapidity with which hyponatremia develops that decides the clinical presentation and not just the levels of serum sodium.

The commonest etiology of hyponatremia in the present study is SIADH followed by renal salt wasting, gastrointestinal loss, cirrhosis of liver, drug induced and cardiac causes. Furthermore, it was observed that patients with SIADH having infectious etiologies especially, tubercular are more likely to develop hyponatremia.

Clinicians need to be aware about the common occurrence of hyponatremia, its early identification and its association with large variety of diseases. In a country like India where disease like tuberculosis is common and remains latent can often present only as symptomatic hyponatremia. Tuberculosis can induce hyponatremia in several ways like local invasion of adrenal glands or pituitary gland, tubercular meningitis and SIADH (via pulmonary infection). Therefore, patients with hyponatremia should be meticulously screened for the presence or absence of tuberculosis. Thus, to conclude, a thorough understanding of the pathophysiological

process of hyponatremia and its associated risk factors is of great importance in prompt and effective treatment of this potentially life threatening condition.

SUMMARY

Hyponatremia is the most common electrolyte disorder in critically ill patients. It is important to recognize this condition as it is a leading cause of morbidity and mortality. This study was aimed at assessing the clinical features, etiology and severity of hyponatremia in critically ill patients admitted to Medical Intensive Care Unit.

The present one year cross sectional observational study was done in the Department of Medicine of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients admitted in MICU with moderate to severe hyponatremia from January 2014 to December 2014 were studied.

The male to female ratio was 1.43:1 with 59% of the patients being males. Most of the patients were aged between 61 to 70 years (29%) and mean age was 58.94 ± 16.10 years. The commonest presentation was vomiting (28%) followed by confusion (26%), seizure (9%) and coma (4%). Nearly half of the study population had altered sensorium (48%). Among co- morbid conditions history of hypertension and diabetes mellitus was noted in 49% and 29% respectively. The commonest system to be involved was central nervous system (43%). With regard to serum sodium levels, 54% of the patients had sodium levels < 120 mEq/L i.e. severe hyponatremia. On the basis of volume status, 50% of patients were euvolemic and had euvolemic hypo-osmolar hyponatremia. In 66 % of the patients, urine sodium levels were ≥ 20 mM. The commonest cause of hyponatremia in the study was SIADH (46%) with infections being the commonest cause of SIADH. The most common form of infection was tuberculosis, found in 57.7% of patients having

infection as the cause of SIADH. Majority (94%) of the patients improved and mortality was noted in 6% of the patients. There was positive association among SIADH and euvolemic hypoosmolar hyponatremia ($p<0.001$) and high urine sodium ($\geq$ 25mM) ($p<0.001$). Also, confusion was noted in significantly higher number of patients with severe hyponatremia ($p<0.001$). No significant association of severity was found with sex ($p=0.642$), age ($p=0.098$), causes of hyponatremia ($p=0.328$) and type of hyponatremia ($p=0.325$) in our study.

Based on these results it may be concluded that, patients presenting with non-specific symptoms like confusion and vomiting should be carefully evaluated for hyponatremia. Further, evaluating for the cause of hyponatremia is equally important, as treating the underlying cause would prevent considerable morbidity and mortality associated with this enigmatic electrolyte disorder. The treating physician should have a high degree of suspicion for tuberculosis as a cause of hyponatremia, as our study found tuberculosis as the commonest infectious cause of SIADH.

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ANNEXURE I – CONSENT FORM

TITLE OF RESEARCH STUDY: "CLINICAL PROFILE OF HYPONATREMIA IN ADULT PATIENTS ADMITTED TO MEDICAL INTENSIVE CARE UNIT OF A TERTIARY CARE HOSPITAL"

Principal investigator

Dr. *** *******
Post Graduate Student,
Department of General Medicine,
J. N. Medical College, Belgaum.**

Introduction and Purpose

Hyponatremia is one of the commonest electrolyte disturbances encountered in medical wards and contributes to substantial morbidity and mortality. However, early recognition and management drastically alters prognosis. Therefore, this observational study can be taken up to explore the clinical profile of hyponatremia and treat the commonly missed etiologies.

Procedure

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons.

Queries

In case of any queries during study or in future you may contact following persons,

1. Dr. ***** ******, Investigator, PG in General Medicine, JNMC, Belgaum. Phone no. ***** ******.
2. Dr. ***** ****** $_{MD}$ Professor and Head of Unit, Dept of General Medicine, JNMC, Belgaum. Phone no. ***** ******
3. Dr. **** ******, Chairperson, JNMC Ethical committee for Human research. Phone no. ***** *****.

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant : _____ Signature / Thumb print _____

Name of the Witness _____ Signature/ Thumb print _____

Investigator Name: _____ Signature :_____

Date: Place:

ANNEXURE II – PROFORMA

Case No: Name:

Age / Sex: In Patient Number:

Address: Occupation:

Complaints at presentation

Nausea	:	Vomiting	:
Lethargy	:	Malaise	:
Confusion	:	Agitation	:
Headache	:	Difficulty to concentrate	:
Seizure	:	Coma	:
Others	:		

Risk Factors

H / O excessive sweating	:
H / O excessive vomiting	:
H / O diarrhea	:
H / O excessive water intake/ beer intake	:
Others	:

Existing Diagnosis

Diabetes	:	Hypertension	:
Hypothyroidism	:	Hypoadrenalism	:
Psychiatric disease	:	Cardiac failure	:
Chronic liver disease	:	Renal disease	:
Others	:		

Admission diagnosis

1)

2)

3)

Physical examination

General condition

Pallor	:	Yes / No
Icterus	:	Yes / No
Lymphadenopathy	:	Yes / No
Cyanosis	:	Yes / No
Clubbing	:	Yes / No
Edema	:	Yes / No

Hydration status

Vitals

Temperature	:
Pulse	:
Respiratory rate	:
Blood pressure	:

Systemic examination

Respiratory System	:
Cardiovascular System	:
Per Abdomen	:
Central Nervous System	:

Investigations

Haemoglobin	:	Total leukocyte count	:
Differential leukocyte count:		ESR	:
Serum creatinine	:	Blood Urea	:
Random Blood Sugar	:	LFT	:
Serum Osmolality	:	Serum sodium	:
Urine Sodium	:	Urine Osmolality	:
Thyroid function test	:	Serum Cortisol	:
Others	:		

Etiology of hyponatremia:

ANNEXURE III – KEY TO MASTER CHART

+	-	Positive
abdo	-	Abdominal
AF	-	Atrial fibrillation
AFB	-	Acid fast bacilli
ARF	-	Acute renal failure
BPH	-	Benign prostatic hypertrophy
CCF	-	Congestive cardiac failure
CKD	-	Chronic kidney disease
CNS	-	Central nervous system
cns	-	Central nervous system
cumm	-	Cubic millimeter
CVA	-	Cerebrovascular accident
cvs	-	Cardiovascular system
E	-	Expired
F	-	Female
GB	-	Gullian Barre syndrome
GI	-	Gastrointestinal
gm	-	Gram
HIV	-	Human immunodeficiency virus
HRCT	-	High resolution computed tomography
I	-	Improved
IHD	-	Ischemic heart disease
M	-	Male

meq/L	-	Milliequivalents per litre
mg/dL	-	Milligrams per deciliter
mM	-	Milli mole
MRI	-	Magnetic resonance imaging
N	-	No
PAH	-	Pulmonary arterial hypertension
PULM	-	Pulmonary
resp	-	Respiratory
RT	-	Right
SAIO	-	Sub acute intestinal obstruction
SBP	-	Spontaneous bacterial peritonitis
SEC	-	Secondary
SIADH	-	Syndrome of inappropriate secretion of antidiuretic hormone
TB	-	Tuberculosis
TSH	-	Thyroid stimulating hormone
UO	-	Urine output
UTI	-	Urinary tract infection
Y	-	Yes
mOsm/Kg	-	Milli Osmole per Kilograms
AS	-	Altered sensorium