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Study On Clinical Spectrum Of Hyponatremia In Hospitalised Patients

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Abstract

Introduction

Hyponatremia is the most commonly encountered electrolyte abnormality in a hospital setting. Recent studies on hyponatremia have been limited to patients with severe hyponatremia, and there has been no consensus on optimal management of hyponatremia. High mortality among the patients of hyponatremia is secondary to the underlying medical condition, rather than the degree of hyponatremia.

Objectives

To study the clinical features, etiology, and treatment modalities of hyponatremia at a tertiary care center.

Methods

The study was conducted at a tertiary care center (katuri medical college and hospital Guntur) from NOV 2018 to OCT 2020. Successive patients of hyponatremia who were admitted to the hospital were included in the study, and additional cases were identified from the hospital laboratory database. These patients were evaluated for the underlying cause of hyponatremia. It included a detailed history and physical examination followed by appropriate laboratory investigations based on the serum osmolality. Patients were followed up till the hyponatremia was corrected, or patients were discharged from the hospital.

Results

100 patients of hyponatremia were included in the study. 46% of the patients were asymptomatic, 33% had lethargy, 28% had postural dizziness, and 19% had abnormal behavior. The overall incidence of hyponatremia was 4.58% in the hospitalized population, whereas its incidence in ICU patients was 22.4%. There

was a wide range of etiologies, most common being diuretic use, vomiting, renal disorder, congestive heart failure (CHF), liver disorder, and SIADH. 43% of patients had multiple causes. Twelve patients of severe symptomatic hyponatremia were treated with Infusion of hypertonic saline, 25% of patients were given loop diuretics with oral supplementation of sodium chloride.

In patients with hypervolemic hyponatremia, the fluid restriction was advised to 44 patients. Oral supplementation of sodium chloride was given in 36 patients, and 64 patients received normal saline. Nine patients included in the study died, 5 of which had advanced cirrhosis of the liver as an underlying cause. One patient developed osmotic demyelination syndrome (ODS).

Conclusion

Hyponatremia is a common problem in hospital inpatients, more so in critically ill ICU patients. The possible cause of hyponatremia should always be sought. The outcome in severe hyponatremia is governed by its etiology, and not by serum sodium level. Treatment with hypertonic saline in severe symptomatic hyponatremia is safe if the recommendation for the rate of correction of hyponatremia is strictly followed.

Introduction

Hyponatremia is defined as a serum sodium level of less than 135meq/L. An abnormal sodium level does not necessarily imply abnormal sodium balance but can be due to abnormal water balance as well. Hyponatremia, an excess of water in relation to sodium in the extracellular fluid, is the most common electrolyte disorder in hospitalized patients and particularly in the elderly. [(1)] Hyponatremia is essential to recognize because of the potential morbidity and mortality. [(2)] The economic impact of hyponatremia on the patient and the health care facility is evident by more prolonged duration of stay, higher risk of death and disability, and increased cost of care. [(3,4)] Identifying the etiology and risk factors for hyponatremia reduces t he incidence of hospitalized patients. It also minimizes the complications associated with hyponatremia and improves the overall cost of health care. There is a lack of Indian data on the clinical spectrum of hyponatremia in the hospital setting and treatment strategies adapted in various clinical studies. Therefore, we planned to undertake this prospective follow-up study in hospitalized patients at our tertiary care center.

Aims and Objectives

1. To study clinical features and etiology of hypo natremia in hospitalized patients.
2. To study treatment modalities of hyponatremia.

Material and Methodology

Source of Data

The study was conducted at katuri medical college and hospital in the period from NOV 2018 to OCT 2020. All admitted patients whose serum electrolytes (serum sodium) had been estimated were identified from the biochemistry laboratory records. Patients with a serum sodium concentration of less than 135 meq/L at any point during the admission were included in the study.

Inclusion Criteria

All adult (age >18 yrs) patients admitted to Katuri medical college and hospital with documented hyponatremia, defined as serum sodium concentration($[Na^+]$) less than 135 meq/L, were included in the study.

Exclusion Criteria

Patients with pseudo hyponatremia (defined by hyponatremia in the absence of any obvious etiology and presence of hyper proteinemia and hyper triglyceridemia) were excluded from the study.

Methodology

1. **Clinical Assessment**

A. Detailed history

This included the history of symptoms of hyponatremia, predisposing factors, and pre-existing illnesses if present. The definition of symptomatic hyponatremia was based on a clinical assessment of symptomatology, including the presence of altered sensorium, lethargy, postural dizziness, and seizures. Sensorium changes comprised memory disturbances, acute confessional states, stupor, delirium, and coma in the absence of dementia, substance abuse, and psychiatric illness. Drugs that can increase the non- osmotic release of antidiuretic hormone (ADH) or potentiate its renal action (ADH- stimulating drugs) were recorded.

History of illnesses causing hyponatremia such as chronic kidney disease, congestive heart failure, chronic liver disease, hypothyroidism, and other conditions that are associated with SIADH such as CNS disease, pulmonary diseases, small cell lung carcinoma, were noted. History of fluid loss as in diuretic use vomiting, diarrhea, excessive sweating was taken in all patients.

B. Physical Examination

Detailed clinical evaluation was done in every patient. The hydration status of the patient was determined by clinical examination. The signs of hypovolemia included orthostatic fall in blood pressure, tachycardia, dry mucous membranes, decreased skin turgor, and decreased peripheral perfusion with a delayed capillary refill more than three seconds. Hypervolemic state was defined by the presence of ascites, anasarca, symmetrical, and pitting pedal edema, and raised jugular venous pressure (JVP). Accordingly, patients were divided into euvolemic, hypovolemic, hypervolemic states.

At the time of diagnosis of hyponatremia detailed CNS examination was done to document the signs of raised ICP (hypertension, bradycardia, and papilloedema), focal neurological deficit, and the mental status of the patient. After the correction of hyponatremia, CNS examination was repeated, and the presence of symptoms such as dizziness, lethargy, altered sensorium, and seizures was attributed to hyponatremia unless there was a medication effect or coexisting medical condition to account for these symptoms. Patients were screened for osmotic demyelination syndrome ODS based on clinical grounds (i.e., the development of confusion, agitation, flaccid, or spastic paralysis during or after correction of hyponatremia) and magnetic resonance imaging was done as a confirmatory test. [87]

2. Investigations

(a) Complete blood count - Total leukocyte count (TLC), differential leukocyte count (DLC), Hemoglobin (Hb), and platelet count.

(b) Routine examination (RE) and microscopic urine examination (ME), and urine specific gravity were done.

(c) Serum sodium – In patients with severe hyponatremia on 3% saline infusion treatment, serum sodium was done once in 6-8 hours. In symptomatic patients, who were not on hypertonic saline treatment, serum sodium was done daily until the correction of hyponatremia. In asymptomatic patients, serum sodium was done every alternate day. An ion-selective electrode system was used to measure serum electrolytes on Rosche 9180 electrolyte analyzer.

(d) Serum glucose levels and blood urea nitrogen (BUN) – for calculation of serum osmolality

(e) Serum osmolality – was calculated by the **formula:**

Serum osmolality = $2([Na^+] + [K^+]) + RBS/18 + BUN/2.8$ mOsm/L (RBS in mg/dL, BUN in mg/dL)

Based on their serum osmolarity, patients were divided into the following groups-

I. Normal osmolarity - 270 – 290mOsm/L

II. Hyper osmolar - >290mOsm/L

III. Hypo-osmolar - <270mOsm/L

(f) Serum cortisol level – in patients suspected to have SIADH.

(g) Urine osmolality – in patients with hypo-osmolar hyponatremia (serum osmolality < 270mOsm/L)

(h) Urine spot sodium - in patients with hypo-osmolar hyponatremia (serum osmolality < 270mOsm/L)

(i) Brain imaging and CSF analysis – in patients presenting with altered sensorium to exclude structural abnormalities and meningeal in fections.

(j) Other investigations like serum protein and lipid profile to exclude pseudo hyponatremia.

SIADH Diagnostic Criteria - The diagnostic criteria used were as described by Verbalis-[40]

Essential criteria

1. Extracellular fluid (ECF) effective osmolality below 270 mOsm/kg water.
2. Inappropriate urinary concentration (>100mOsm/kg).
3. Clinical euvolemia (absence of signs of hypovolemia and hyper volemia).
4. Increased urinary [Na^+] while on a normal salt and water intake.
5. Absence of thyroid, pituitary, adrenal, diuretic use, or renal insufficiency.

Supplemental criteria for SIADH

1. Abnormal water load test (inability to excrete at least 90% of 20 ml/kg water load in 4 h and failure to dilute urinary osmolality to below100mOsm/kg).
2. Plasma AVP level inappropriately raised relative to plasma osmolality.
3. There is no significant correction of plasma [Na^+] with volume expansion, but improvement occurred after fluid restriction.

3. Management and Outcome Assessment

Based on serum sodium levels, patients with hyponatremia were classified into the following categories:

Category	Serum sodium concentration
(i) Mild hyponatremia-	131 - 134meq/L
(ii) Moderate hyponatremia-	120 - 130meq/L
(iii) Severe hyponatremia-	<120meq/L

4. Treatment Strategy

Decision on the treatment modality of hyponatremia was based on the cause and severity of hyponatremia and the presence of neurological symptoms of hyponatremia.

(i) Fluid restriction is defined as total fluid intake in 24 hrs equal to the volume of urine output of the previous 24 hrs. Fluid restriction was advised in patients with hyper volemic hyponatremia as caused by chronic liver disease, CHF, renal disorders, and patients with SIADH.

(ii) Oral sodium supplementation- was given in patients with asymptomatic euvolemic and hypovolemic hyponatremia with a history of inadequate intake in the past. Oral sodium chloride supplementation was also given to all the patients receiving hypertonic saline after symptomatic improvement and when oral intake could be resumed. Supplemental sodium chloride was added to daily dietary intake in the dose of 15-20 g/day in 3-4 divided doses.

(iii) Normal saline (0.9% NaCl) – hypovolemic patients were treated with normal saline. Normal saline was also given as part of fluid therapy, as in cases of febrile illnesses, vomiting, and diarrhea.

(iv) Loop diuretic- loop diuretic was given for free water excretion in cases of hypervolemic hyponatremia and SIADH.

(v) Hypertonic (3%) saline- Patients with neurological symptoms due to severe hyponatremia with either

hypovolemic or euvolemic status were treated with hypertonic saline, with an aim to increase serum sodium level by 8meq/L in 24 hrs.

5. Data collection

For all patient clinical and demographic detail, final diagnosis, investigations, and management were recorded onto a standard data collection sheet as per the study performa and later transferred to a Microsoft Excel spreadsheet for analysis.

Statistical analysis

Data were recorded on a predesigned performa and managed in a Microsoft Excel spreadsheet. All the entries were double-checked for any possible keyboard error. Data so collected were systematically analyzed. Data are presented as frequency distribution and simple percentages. Descriptive statistics, i.e., mean and standard deviation has been calculated for the continuous variables. Categorical variables are expressed as percentages

Results

Table 1. Causes of Hyponatraemia

CAUSES	NO
Acute gastroenteritis	8
Febrile illness	8
Liver disease *	4
GI malignancy**	4
Increased ICP***	2
Chemotherapy	1
Alcohol-induced pancreatitis	1
Renal disorder	1
SAIO	1

Table 2. Co-Morbid Cordings Leading to Hyponatraemia

CO-MORBID CONDITIONS	No
Malignancy	5
Liver disease	4
Febrile illness	4
Uremia	3
Alcohol-induced pancreatitis	2
Gastroenteritis	2
Odynophagia	1

Discussion

Hyponatremia is the most common electrolyte disturbance seen in hospital practice. It is more common in elderly patients with multiple medical comorbidities. Hyponatremia has been associated with considerable morbidity and mortality in many chronic diseases, most notably in patients with congestive heart failure and cirrhosis of the liver. Hyponatremia also leads to increased health care costs. The majority of these costs are attributable to the incremental resource utilization for patients who were not admitted specifically for hyponatremia, but whose hospitalization was prolonged due tohyponatremia.

This study had included 64 patients of hyponatremia admitted in general medical and surgical wards and 36 critically ill patients admitted to ICU.

Previous studies in hospitalized patients showed the incidence of hyponatremia was about 1% to 6% In this study, the overall incidence of hyponatremia was 4.58%. A 5-year retrospective study of 2,188 patients, at the time of admission to the intensive care unit, Bennani et al[3], found the incidence of hyponatremia to be 14% while DeVita et al[4.] Found the incidence of hyponatremia in ICU to be 29.6%. Incidence of hyponatremia in ICU patients in this study was 22.4%. The incidence of hyponatremia has been shown to have a direct correlation with age. In our study, patients of age 50 to 80 yrs were 65%. Multiple comorbidities like Diabetes Mellitus and Hypertension are present in this age group treatment, of which predisposes a patient to hyponatremia. Diuretics use are also more common among elderly patients, which has been a major cause of hyponatremia in hospitalized patients. Hawkins et al. found that increasing age, after adjusting for sex, was independently associated with both hyponatremia at presentation and hospital-acquired hyponatremia.

In the present study, hyponatremia prevalence was more in male patients with a male: female ratio of 1.8:1 (63 males and 37 females). This is because the number of patients admitted in the male medical and surgical wards outnumbered the patients admitted in the correspondingfemalewards.Hawkinsetal[5.]

Diuretic use was the most common cause for hyponatremia in our study, present in 35 (35%) of the total patients in the study out of which 19 patients were on thiazide diuretics (54.3%), nine patients were on a combination of the loop diuretic, and spironolactone (25.74%) and seven patients were on loop diuretics (20%). Thiazide diuretics are a common cause of severe hyponatremia. Up to a third of elderly patients taking a thiazide at hospital admission are hyponatremia, and 14% of patients prescribed a thiazide diuretic in primary care have sodium below the normal range. Severe hyponatremia occurs mostly with thiazide diuretics rather than loop diuretics.

Vomiting is one of the strongest known stimuli for ADH release. This was the second most common cause of hyponatremia in our study after the diuretic use (29%). Vomiting in our patients was associated with infective illnesses (16 patients; gastroenteritis, enteric fever, viral fever), systemic illnesses (acute and chronic liver diseases- 4 patients, renal disorder- 1 patient), gastrointestinal obstruction (4 patients), drug-induced (2 patients) and increased ICP (2 patients). It was also associated with inadequate intake and diarrhea in 8 (38%) and 5 (23.8%) of these patients respectively.

Inadequate nutritional intake secondary to various other comorbidities was a significant risk factor in this study. Total 21 (21%) patients had a history of poor intake, which was associated with multiple causes like a malignancy in 5 patients, liver diseases in 4 patients, febrile illnesses in 4 patients, uremia in 3 patients, alcohol abuse in 2 patients, and odynophagia secondary to a submandibular abscess in 1 patient. None of the studies have considered vomiting and inadequate intake as an etiology or risk factor for hyponatremia in the available literature. Thus, our study highlights the importance of eliciting a history of inadequate nutritional intake and vomiting in hyponatremia patients.

Thirteen (13%) patients in the present study fulfilled the diagnostic criteria for SIADH. The incidence is comparable to the available literature on hyponatremia in hospitalized patients. In a study by Saeed et al[8.] incidence of SIADH among hyponatremia patients was 14.03%, while in a study by Huda et al., it was 19.8%. In our study, five patients had drug-induced SIADH (2 selective serotonin reuptake inhibitors, 2 Carbamazepine, and one olanzapine), four patients had SIADH dueto

pulmonary disease (2cases of pneumonia, one bronchogenic carcinoma, and one tuberculosis), three patients had primary neurological disorders (2 cases of CNS tuberculosis and 1 case of Guillain Barre Syndrome), and one patient had SIADH due to lung metastasis with carcinoma prostate. In a few patients with severe hyponatremia who were started on new treatment with hypertonic saline and diuretics, it was not possible to document the presence of SIADH. Therefore in our study, a few patients on diuretic might have had concomitant SIADH, which could not be established. At present, there are no guidelines on the appropriate washout period for diuretics before necessary biochemical investigations to demonstrate SIADH can be performed.[92]

The patients who developed postoperative hyponatremia in our study were given hypotonic fluids (5% dextrose). Miller et al., in their study on hyponatremia in nursing home patients, concluded that increased fluid intake or low sodium content in enteral feeding could lead to hyponatremia. [9]

In our study, 31 (31%) patients had severe hyponatremia. Diuretic use was the most common etiology associated with severe hyponatremia (13%). It included two patients with loop diuretic use, seven patients with a combination of loop diuretic and spironolactone, and four thiazide diuretic patients. All the patients using a combination of loop diuretic and spironolactone who developed severe hyponatremia had an additional contributory factor for hyponatremia (5 with liver disease, 1 with vomiting, and one was in the postoperative period). Other causes associated with severe hyponatremia were vomiting in 8 patients, renal disorders in 6 patients, heart failure in 5 patients, liver disorders in 5 patients, and SIADH in 5 patients. Fourteen cases of severe hyponatremia had single etiology, which included 4 cases of diuretic use (all thiazide diuretics), 4 cases of heart failure, 3 cases of SIADH, 2 cases of renal disorder, and 1 case of poor intake secondary to systemic illness (systemic lupus erythematous). In a study by Clayton et al. on severe hyponatremia in a hospitalized patients, 25 out of 105 patients had single etiology for severe hyponatremia, which included thiazide diuretics in 11 patients, liver disease in 4 patients, CNS lesion/stroke in 2 patients, hypopituitarism/Addison's disease in 2 patients, lower respiratory tract infection in 1 patient, Carbamazepine in 1 patient and unknown cause in another four patients.

In our study, 43% of the patient had multiple etiological factors for hyponatremia. In recent studies, varying proportions of the patient have been associated with multiple etiologies of hyponatremia.

In a study by Clayton et al., 75% of the patients of hyponatremia had multiple etiologies while in a study by Nzerue et al., only 10.9% of the patients had multiple etiological factors These studies emphasize the importance of establishing the various factors responsible for hyponatremia in the patient to take relevant corrective measures during the treatment.

Treatment of hyponatremia in our study was decided by the severity of hyponatremia, presence of symptoms, and underlying disorders. Patients with clinical evidence of dehydration, as in patients with vomiting, diarrhea, and febrile illnesses and no neurological symptoms of hyponatremia were treated with normal saline infusion. Patients with dilutional hyponatremia were treated with fluid restriction (intake equal to the urine output in previous 24 h) and loop diuretics for promoting excretion of free water. Patients with SIADH were treated with fluid restriction and loop diuretics and oral sodium chloride supplementation for free water excretion. All other patients with moderate or

asymptomatic hyponatremia were treated with oral sodium chloride supplementation.

In our study, 64% of the patients received normal saline, 44% were on fluid restriction, 36% were given oral sodium chloride supplementation, and 25% received loop diuretics. There are considerable differences in the treatment strategies for hyponatremia in recent studies on hyponatremia in hospitalized patients. In a study by Hoorn et al. on severe hyponatremia in hospitalized patients, 29% of patients were given normal saline, 9% of patients were advised fluid restriction, 10% of patients received oral sodium chloride supplementation, and 19% patients received no therapy for hyponatremia, whereas in the study by Nzerue et al. 82% of the patients received normal saline, 9% of patients were given fluid restriction, while 6% were treated with other treatment modalities such as withdrawal of drugs causing hyponatremia.

Conclusion

Hyponatremia is a common electrolyte abnormality found in hospitalized patients in general medical and surgical wards. It is more common in elderly patients, and critically ill patients admitted to the ICU. Hypertension and Diabetes Mellitus as pre-existing comorbidity was present in the majority of patients, and it predisposed the patients to hyponatremia.

Thiazide diuretics were the single most important etiology of hyponatremia. Vomiting and poor intake were also significant causes of hyponatremia in this study. Other major causes of hyponatremia were renal disorders, SIADH, CHF, and chronic liver disease. Hyponatremia was found to be related to multiple etiological factors in a large number of patients.

Treatment of hyponatremia with hypertonic saline should be restricted to patients with severe hyponatremia and those with neurological symptoms of hyponatremia. Treatment with hypertonic saline is safe, provided gradual correction of hyponatremia is followed.

Osmotic demyelination syndrome is a rare complication related to the treatment of hyponatremia. It should be suspected in a case of hyponatremia who develop fresh neurological deficits while on treatment or after treatment with hypertonic saline.

Severe hyponatremia is associated with considerable mortality in patients with underlying medical diseases as advanced cirrhosis.

A systematic approach to the diagnosis of hyponatremia with the application of simple diagnostic algorithms, history, clinical examination, and laboratory findings to establish the mechanism of hyponatremia can significantly improve the assessment and management of hyponatremia.

Summary

Hyponatremia is the most common electrolyte disorder in hospitalized patients, particularly in the elderly. Hyponatremia is essential because of the potential morbidity, mortality, and the economic impact on the patient and health care. Studying the etiology, risk factors, and management of hyponatremia in hospitalized patients will help in reducing its incidence and minimize the complications associated with hyponatremia.

The study was conducted at a tertiary care center (katuri medical college and hospital, Guntur). Successive patients of hyponatremia who were admitted to the hospital were included in the study, and additional cases were identified from the hospital laboratory database. These patients were evaluated for the underlying cause of hyponatremia, which included a detailed history and physical examination, followed by appropriate laboratory investigations based on serum osmolality.

One hundred patients of hyponatremia were included in the study. 46% of the patients were

asymptomatic, and 19% had abnormal behavior. The overall incidence of hyponatremia was 4.58% in the hospitalized population, whereas its incidence in ICU patients was 22.4%. There was a wide range of etiologies, most common being diuretic use (35%), vomiting (29%), poor intake (21%), renal disorder (19%), SIADH (13%), congestive heart failure (8%), and liver disorder (8%). 43% of patients had multiple causes. Twelve patients of severe symptomatic hyponatremia were treated with hypertonic saline infusion, 25% patients were given loop diuretics with oral supplementation of sodium chloride for free water excretion in SIADH cases and patients with hypervolemic hyponatremia, the fluid restriction was advised to 44 patients, oral supplementation of sodium chloride was given in 36 patients, and 64patients Five of which had advanced cirrhosis of the liver as the underlying cause. One patient developed osmotic demyelination syndrome (ODS).

Hyponatremia is a common problem in hospital inpatients, more so in critically ill ICU patients. The possible cause of hyponatremia should always be sought as an outcome in severe hyponatremia is governed by etiology, and not by the serum sodium level. Vomiting and poor nutritional intake were associated with a large proportion of the patients in this study, which have not been considered the etiology of hyponatremia in the available literature. Treatment of severe symptomatic hyponatremia with hypertonic saline is safe if the recommendation for the rate of correction of hyponatremia is strictly followed. Osmotic demyelination syndrome is a rare complication related to the treatment of hyponatremia. It should be suspected in a case of hyponatremia who develop fresh neurological deficits while on treatment or after correction of hyponatremia.

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