

CLINICAL SPECTRUM OF HYPONATRAEMIA IN TERTIARY CENTRESuresh Chincholi¹, Sangram Biradar², Syed Akbar³, Mohammad Mushtaq Aejaaz⁴, Rahul Ladda⁵¹Professor and HOD, Department of Medicine, Mahadevappa Rampure Medical College, Kalaburagi.²Associate Professor, Department of Medicine, Mahadevappa Rampure Medical College, Kalaburagi.³Postgraduate Student, Department of Medicine, Mahadevappa Rampure Medical College, Kalaburagi.⁴Postgraduate Student, Department of Medicine, Mahadevappa Rampure Medical College, Kalaburagi.⁵Postgraduate Student, Department of Medicine, Mahadevappa Rampure Medical College, Kalaburagi.**ABSTRACT****BACKGROUND**

Hyponatraemia is defined as a serum sodium level less than 135 mEq/L. High mortality among the patients of hyponatraemia is secondary to the underlying medical condition. Frequency is high in elderly patients.

MATERIALS AND METHODS

The study was conducted at a tertiary care centre (Basaveshwar Teaching and General Hospital, Gulbarga), from the period September 2014 to August 2016. These patients were evaluated for the underlying cause of hyponatraemia, which included detailed history and physical examination followed by appropriate laboratory investigations. Patients were followed up till the hyponatraemia was treated or patients were discharged from the hospital.

RESULTS

100 patients of hyponatraemia were included in the study. 46% of the patients were asymptomatic. 33% patients had lethargy, 28% patients had postural dizziness and 19% had abnormal behaviour. Overall incidence of hyponatraemia was 4.58% in the hospitalised population, whereas its incidence in ICU patients was 22.4%. Twelve patients of symptomatic severe hyponatraemia 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 in patients with hypervolaemia, hyponatraemia, fluid restriction was advised to 44 patients, oral supplementation of sodium chloride was given in 36 patients and 64 patients received normal saline. 9 patients included in the study died, 5 of which had advanced cirrhosis of liver as underlying cause. One patient developed Osmotic Demyelination Syndrome (ODS).

CONCLUSION

The possible cause of hyponatraemia should always be sought as outcome in severe hyponatraemia is governed by aetiology, and not by the serum sodium level. Treatment of severe symptomatic hyponatraemia with hypertonic saline is safe if recommendation for the rate of correction of hyponatraemia is strictly followed.

KEYWORDS

Hyponatraemia, Syndrome of Inappropriate ADH Secretion, SIADH, ICU, Osmotic Demyelination Syndrome.

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BACKGROUND

Hyponatraemia is defined as a serum sodium level less than 135 mEq/L. An abnormal sodium level does not necessarily imply abnormal sodium balance, but can be due to abnormal water balance as well. Hyponatraemia, an excess of water in relation to the sodium in the extracellular fluid is the most common electrolyte disorder in hospitalised patients and particularly so in the elderly.¹ Hyponatraemia is very common disorder occurring in up to 22% of hospitalised

patients.² The underlying pathophysiology for the exaggerated or "inappropriate" AVP response differs in patients with hyponatraemia as a function of their ECFV. Hyponatraemia is thus subdivided diagnostically into three groups depending on the clinical history and volume status, i.e. "hypovolaemic," "euvolaemic" and "hypervolaemic." Hyponatraemia is important to recognise because of the potential morbidity and mortality.³ The economic impact of hyponatraemia on the patient and the healthcare facility is evident by longer duration of stay, higher risk of death and disability and increased cost of care.^{4,5}

Aims and Objectives of the Study-

To know the incidence, aetiology, clinical features and treatment outcomes of hyponatraemia at a tertiary care centre.

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MATERIALS AND METHODS

Source of Data

The study was conducted at Basaveshwar Teaching and General Hospital, Gulbarga, in the period of September 2014 to August 2016. All admitted patients whose serum electrolytes had been estimated were identified from the biochemistry laboratory records. Those patients with a serum sodium concentration 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 Basaveshwar Teaching and General Hospital, Gulbarga, with documented hyponatraemia defined as serum sodium concentration (Na) less than 135 mEq/L were included in the study.

Exclusion Criteria

Patients with pseudohyponatraemia (defined by hyponatraemia in the absence of any obvious aetiology and presence of hyperproteinaemia and/or hypertriglyceridaemia) were excluded from the study.

METHODOLOGY

Clinical Assessment

(a) Detailed History

This included history of symptoms of hyponatraemia. The definition of symptomatic hyponatraemia was based on a clinical assessment of symptomatology including the presence of altered sensorium, postural dizziness, lethargy and seizures. Drugs that can increase the nonosmotic release of Antidiuretic Hormone (ADH) or potentiate its renal action (ADH- stimulating drugs) were recorded. History of illnesses causing hyponatraemia such as CHF, CKD, chronic liver disease, hypothyroidism and other.

(b) Physical Examination

The signs of hypovolaemia included tachycardia, orthostatic falls in blood pressure, decreased skin turgor, dry mucous membranes and decreased peripheral perfusion with a delayed capillary refill more than 3 seconds. Hypervolaemic state was defined by the presence of anasarca, ascites, symmetrical and pitting pedal oedema and raised Jugular Venous Pressure (JVP).

At the time of diagnosis of hyponatraemia, detailed CNS examination was done to document the signs of raised ICP (bradycardia, hypertension and papilledema), mental status of the patient and other focal neurological deficit. CNS examination was repeated after the correction of hyponatraemia. Patients were screened for osmotic demyelination syndrome ODS based on clinical grounds, (i.e., the development of confusion, agitation and flaccid or spastic paralysis during or after correction of hyponatraemia) and magnetic resonance imaging was done as confirmatory test.

Investigations

- Complete blood count.
- Urine Routine Examination (RE) and Microscopic Examination (ME) and specific gravity.

- Serum sodium- Serum sodium was done 6-8 hourly in patients with severe hyponatraemia on 3% saline infusion. Serum electrolytes were measured by an ion selective electrode system on Roche 9180 electrolyte analyser.
- Serum Blood Urea Nitrogen (BUN) and glucose levels.
- Serum osmolality was calculated.
 - Normality osmolality - 270-290 mOsm/L.
 - Hyperosmolar - >290 mOsm/L.
 - Hypo-osmolar - <270 mOsm/L.
- Serum cortisol level in patients suspected to have SIADH.
- Urine osmolality in patients with hypo-osmolar hyponatraemia (serum osmolality <270 mOsm/L).
- Urine spot sodium in patients with hypo-osmolar hyponatraemia (serum osmolality <270 mOsm/L).
- Brain imaging and CSF analysis.
- Others- Serum protein and lipid profile to exclude pseudohyponatraemia.

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

Essential Criteria-

- Extracellular Fluid (ECF) effective osmolality below 270 mOsm/kg water.
- Inappropriate urinary concentration (>100 mOsm/kg).
- Clinical euvolaemic (absence of signs of hypovolaemia and hypervolaemia).
- Increased urinary (Na⁺) while on a normal salt and water intake.
- Absence of adrenal, thyroid, pituitary or renal insufficiency or diuretic use.

Supplementation Criteria

- Abnormal water load test (inability to excrete at least 90% of 20 mL/kg water load in 4 hrs. and/or failure to dilute urinary osmolality to below 100 mOsm/kg).
- Plasma AVP level inappropriately raised relative to plasma osmolality.
- No significant correction of plasma (Na⁺) with volume expansion, but improvement after fluid restriction.

Management and Outcome Assessment

Patients with hyponatraemia were classified based on serum sodium levels into following categories-

Category Serum Sodium Concentration

- Mild hyponatraemia 131-134 mEq/L.
- Moderate hyponatraemia 120-130 mEq/L.
- Severe hyponatraemia <120 mEq/L.

Treatment Strategy

- Fluid restriction.
- Oral sodium supplementation.
- Normal saline (0.9% NaCl).
- Loop diuretics.
- Hypertonic (3%) saline.

Statistical Analysis- Data were recorded on a predesigned proforma and managed in a Microsoft excel spreadsheet. 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 AND DISCUSSION

Incidence- A total 2184 patients were admitted to the medical and surgical wards and ICU of Basaveshwar Teaching and General Hospital, Gulbarga, between the period September 2014 to August 2016, 100 patients out of these developed hyponatraemia giving an overall incidence of 4.58%. Hyponatraemia in ICU patients was studied in the period of 4 months March 2015 to June 2015, 36 out of total 161 patients admitted in ICU during this period developed hyponatraemia. Overall, incidence of hyponatraemia in ICU was 22.4%.

Clinical Profile

- 1. Age Distribution-** Mean age was 57.21 years. Number of patients in different age groups are shown in Figure 1.
- 2. Sex Distribution-** There were 37 females and 63 males out of total 100 patients in this study.
- 3. Symptoms-** Frequency of clinical symptoms is as shown in Figure 2. None of the patients had seizures or coma due to hyponatraemia.
- 4. Pre-Existing Illnesses-** The incidence and distribution of pre-existing illnesses is as shown in Figure 3. Figure 4 shows incidence of comorbid conditions with diabetes.
- 5. Aetiology of Hyponatraemia-** 65 patients in this study had hypo-osmolar, hyponatraemia, 31 patients had normal serum osmolality and 4 patients had hyperosmolar hyponatraemia (due to hyperglycaemia and azotaemia).

Diuretic use was the most common cause of hyponatraemia in this study. Total 35 (35%) patients were taking diuretics. Out of these, 19 patients were on thiazide and diuretics, 9 were taking a combination of loop diuretic and spironolactone and 7 patients had taken only loop diuretic (Figure 5).

The incidence and distribution of aetiological factors of hyponatraemia are depicted in Figure 6 as under.

In 57 patients, there was single aetiology of hyponatraemia while in 43 patients more than one contributory factors for hyponatraemia were responsible. Out of these 43 patients, 37 patients had 2 contributory factors, 5 patients had 3 contributory factors and 1 patient had 4 contributory factors for hyponatraemia. Distribution of single aetiology of hyponatraemia is depicted in Figure 7.

Spectrum of Severe Hyponatraemia- 31 patients in this study had severe hyponatraemia, 69 patients had mild or moderate hyponatraemia. Cause of severe hyponatraemia have been depicted in Figure 8.

Treatment- The various strategies adopted for the patients for correction of hyponatraemia has been summarised in Figure 9.

- 6. Potassium Replacement-** Total 13 patients developed hypokalaemia due to co-morbid conditions like vomiting and diarrhoea or due to diuretic use. These patients were given oral potassium supplements.
- 7.** The aim was to correct the serum sodium levels gradually by increasing sodium levels at 8-10 mEq/L/day. The aim was achieved in most of the patients.
- 8. Duration of Correction of Hyponatraemia-** Mean duration of correction of hyponatraemia ranged from 3 days to 17 days and mean duration of correction was 6 days.
- 9. Treatment Related Complications-** As detailed below, one patient treated with hypertonic saline developed osmotic demyelination syndrome with characteristic clinical and MRI features. No other complications were noted in other patients.
- 10.** Ten patients had persistent hyponatraemia at the time of discharge from the hospital. It was associated with diuretic use in 3, CHF in 2, SIADH in 2, liver disease in 1, poor intake in 1 and colostomy fistula in 1 patient.

Complications of Treatment of Hyponatraemia- One patient of severe hyponatraemia during the study had a rare renal salt wasting state. This patient had presented initially to another institute with progressively increasing quadriparesis with preserved deep tendon jerks, intermittent carpopedal spasms and one episode of generalised seizures following a short febrile illness and acute gastroenteritis. The patient was treated with hypertonic saline for severe hyponatraemia (serum sodium 113 mEq/L) for two days outside our hospital. However, there was no improvement in the clinical status of the patient and hyponatraemia persisted despite treatment with hypertonic saline. Patient was thereafter referred to our hospital for further management. This patient had significant past history of developing episodic carpopedal spasms after episodes of acute gastroenteritis and febrile illnesses. On detailed evaluation, she was found to have concomitant hypokalaemia (2.4 mEq/L), hypomagnesaemia (0.80 mg/dL) and hypocalcaemia (5.90 mg/dL) with urinary magnesium wasting and metabolic alkalosis. She was diagnosed to have renal salt wasting secondary to Gattaman's syndrome, an autosomal recessive disease characterised by mutations in the gene coding for the thiazide-sensitive NaCl cotransporter in the distal tubule. Her quadriparesis failed to improve despite correction of all the electrolyte deficiencies. MRI brain was done, which showed characteristic bat's wing appearance of Central Pontine Myelinolysis (CPM), which was presumably related to the hypertonic saline treatment.

Mortality- A total of 9 (9%) patients in this study died during the study period from factors other than hyponatraemia. Most common cause was advanced cirrhosis of liver present in 5 patients. 1 patient died due to urinary tract infection leading to sepsis. Other causes responsible for death were HIV infection with tubercular meningitis in one patient, carcinoma ovary with multiple metastasis in one patient and end-stage kidney disease in one patient. Out of 31 patients of severe hyponatraemia in our study, 6 patients died, thus giving a mortality of 19.3% among the patients of severe hyponatraemia.

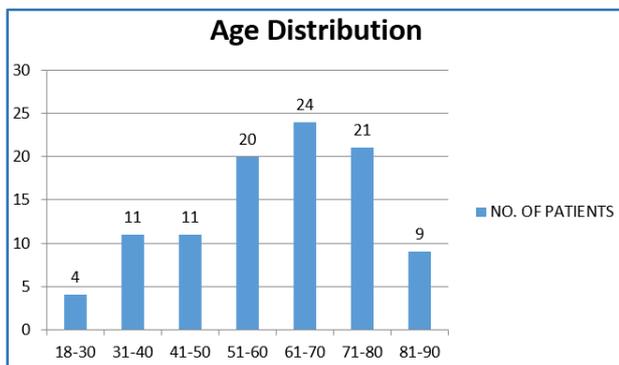


Figure 1. Age Distribution of Patients (in Numbers)

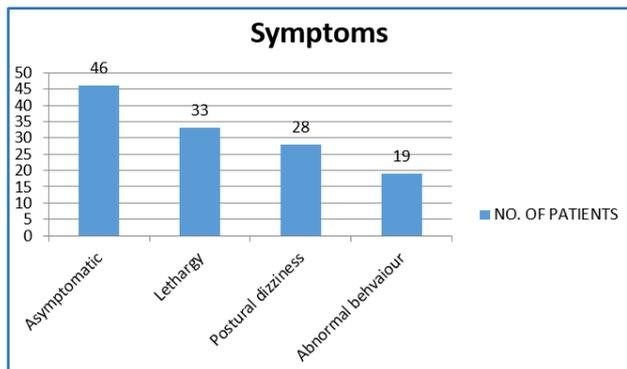


Figure 2. Distribution of Symptoms of Hyponatraemia in Numbers (Several Patients had More than One Symptoms)

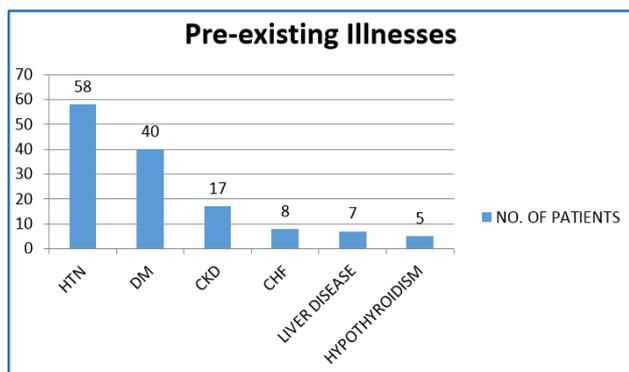


Figure 3. Distribution of Pre-Existing Illnesses (in Numbers)

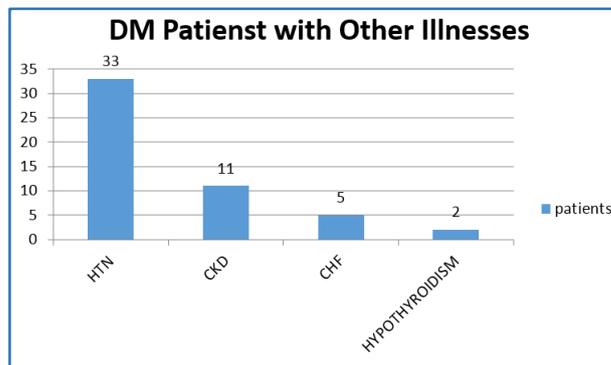


Figure 4. Diabetic Patients with Other Illnesses (in Numbers)

(Note- HTN- Hypertension, CKD- Chronic Kidney Disease, CHF- Congestive Heart Failure).

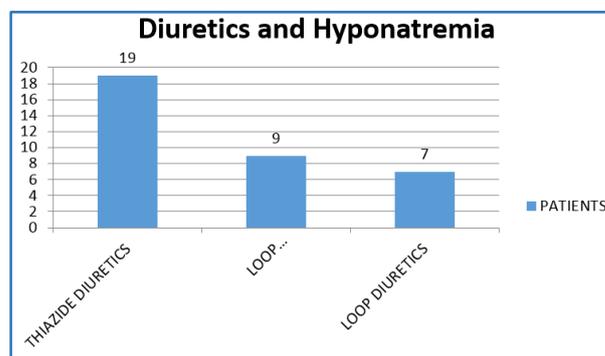


Figure 5. Diuretic-Induced Hyponatraemia (in Numbers)

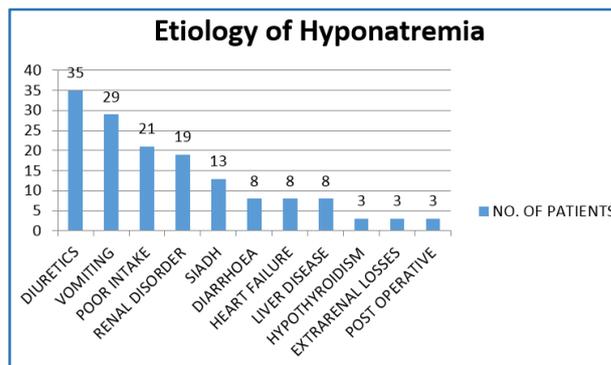


Figure 6. Distribution of Aetiology of Hyponatraemia (in Numbers)

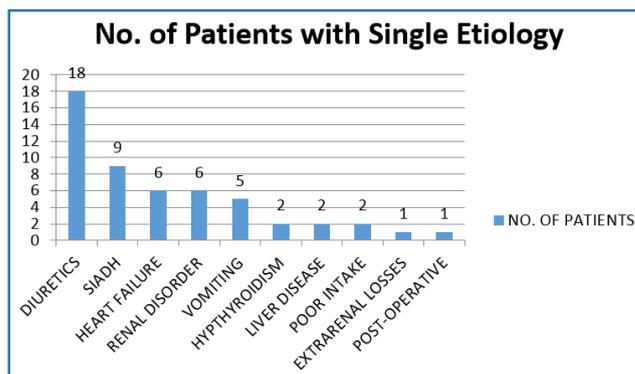


Figure 7. Number of Patients with Single Cause of Hyponatraemia

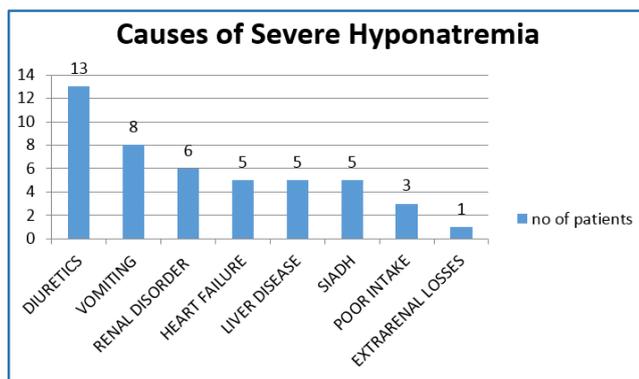


Figure 8. Cause of Severe Hyponatraemia (in Numbers)

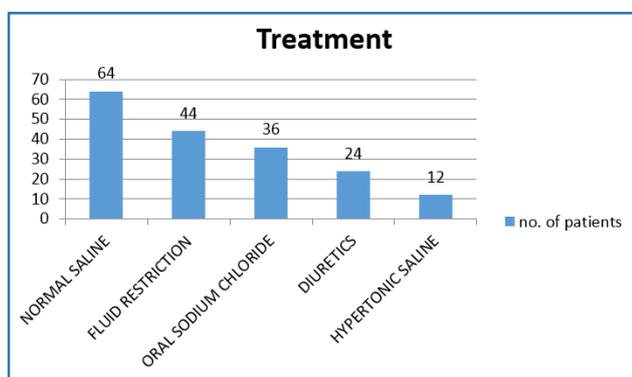


Figure 9. Treatment Strategy for Correction of Hyponatraemia (in Numbers)

DISCUSSION

Hyponatraemia is the most common electrolyte disturbance seen in hospital practice. It is more common in the elderly patients with multiple medical comorbidities.⁶ Hyponatraemia has been associated with considerable morbidity and mortality in many chronic diseases, most notably in patients with CHF⁷ and cirrhosis of liver.⁸ In previous studies, incidence of hyponatraemia in hospitalised patients was found to be about 1% to 6%.^{9,10,11} In this study, overall incidence of hyponatraemia was 4.58%. In a 5-year retrospective study of 2188 patients, Bennani et al¹¹ found the incidence of hyponatraemia to be 14% at the time of admission to the intensive care unit while DeVita et al¹² found the incidence of hyponatraemia in ICU to be 29.6%. In this study, incidence of hyponatraemia in ICU patients was 22.4%.

Incidence of hyponatraemia has been shown to have direct correlation with age.⁶ In our study, 65% of the patients were 50 to 80 yrs. old. In the present study, prevalence of hyponatraemia was more in male patients with male:female ratio of 1.8:1 (63 males and 37 females). In the same study by Hawkins et al when comparisons were made by sex and after adjusting for age, male sex was weakly associated with mild or moderate, but not severe hyponatraemia.¹³ Female sex has been shown to be a risk factor for hyponatraemia induced by psychotropic medications or diuretics.⁶

In this study, 54% of the patients had manifestations of hyponatraemia at presentation. A major population (46%)

of the patients in the study did not have evident clinical manifestations of hyponatraemia. This can be possibly due to the reason that acute hyponatraemia (hyponatraemia of <48 hrs. duration) is less frequent than chronic hyponatraemia (>48 hrs. duration) in which symptoms are ameliorated by the phenomenon of cerebral adaptation of hyponatraemic state.¹⁴ In study of severe hyponatraemia in Queen’s Medical Centre, UK, by Clayton et al, 36.2% patients had neurological symptoms attributable to the hyponatraemia at presentation.¹⁵ In our study, hypertension was a major risk factor for hyponatraemia due to diuretic use in elderly patients. The studies on hyponatraemia have not demonstrated direct correlation between hyponatraemia and hypertension, although correlation of hyponatraemia with age¹³ and diuretic use is evident.¹⁶

Diuretic use were the most common cause for hyponatraemia in our study. Saeed et al studied hyponatraemia in hospitalised patients and in 19 out of 57 patients (33.3%), it was associated with diuretic use.¹⁷ Thiazide diuretics are a common cause of severe hyponatraemia.¹⁸ Up to a third of elderly patients taking a thiazide at hospital admission are hyponatraemic and 14% of patients prescribed a thiazide diuretics in primary care have a sodium below the normal range.^{19,16} Severe hyponatraemia occurs almost exclusively with thiazide rather than loop diuretics.²⁰ In our study, 7 out of 31 patients of severe hyponatraemia were on thiazide diuretic. In a study by Huda et al, 14 out of 22 (63.6%) patients of hyponatraemia on diuretics were taking thiazide diuretics.²¹ Vomiting is one of the strongest known stimuli for ADH release.²²

Thirteen (13%) patients in present study fulfilled the diagnostic criteria for SIADH.²³ The incidence is comparable to the available literature on hyponatraemia in hospitalised patients. In the study by Saeed et al, incidence of SIADH among hyponatraemia patients was 14.03% while in study by Huda et al, it was 19.8%.^{17,21} Van Amelsvoort et al had found that carbamazepine led to hyponatraemia in patients with epilepsy, neuralgia, mental retardation and psychiatric disorders with a frequency varying from 4.8 to 40%.⁶ In our study, 2 (2%) patients and carbamazepine associated hyponatraemia.

Other causes of hyponatraemia in this study included postoperative (3%) and extra-renal losses (3%). The study by Clayton postoperative hyponatraemia occurred in 2% of the patients.¹⁵ The patients who developed postoperative hyponatraemia in our study were given hypotonic fluids (5% dextrose). Miller et al in their study on hyponatraemia in nursing home patients concluded that increased fluid intake or low sodium content in enteral feeding can lead to hyponatraemia.⁷

In our study, 43% of the patients had multiple aetiological factors for hyponatraemia. Treatment of hyponatraemia in our study was decided by the severity of hyponatraemia, presence of symptoms and underlying disorders.

In our study, 64% of the patients received normal saline, 44% of the patients were on fluid restriction, 36% patients

were given oral sodium chloride supplementation and 25% patients received loop diuretics. There are considerable difference in the treatment strategies for hyponatraemia in recent studies on hyponatraemia in hospitalised patients. In study by Hoorn et al on severe hyponatraemia in hospitalised patients, 29% patients were given normal saline, 9% patients were advised fluid restriction, 10% patients received oral sodium chloride supplementation and 19% patients received no therapy for hyponatraemia whereas in study by Nzerue et al 82% of the patients received normal saline, 9% patient were given fluid restriction while 6% patients were treated with other treatment modalities such as withdrawal of drug-causing hyponatraemia.^{8,3} In our study, hypertonic (3%) saline was used for the treatment of severe symptomatic hyponatraemia. 12 patients (12%) were given hypertonic saline infusion. The aim was gradual correction of hyponatraemia with increase of serum sodium by 8 mEq/L in 24 hrs. The level of correction was usually within the recommended level in most patients. In study by Nzerue et al, 3% patients received hypertonic saline while in study by Hoorn et al, 5% of the patients received hypertonic saline.^{3,8} Therefore, the use of hypertonic saline in the present study has been limited to 3% saline and it commensurate with the available literature. The incidence of Osmotic Demyelination Syndrome (ODS) following treatment of hyponatraemia has been very rare.²⁴ In this study, one patient was diagnosed to have ODS when she was evaluated for persistent quadriparesis. Hypokalaemia has also been described as a risk factor for ODS by JW Lohr.²⁵

The mortality in patients with severe hyponatraemia has been found to be between 20 to 27% in literature.^{3,21} The overall mortality among patients of hyponatraemia in our study was 9% and 19.3% among patients with severe hyponatraemia. Mortality was not directly related to hyponatraemia, but to the severity of the underlying medical condition in the patients. In 2005, Huda et al in their study found that there was 27% mortality among patients of severe hyponatraemia.²¹ However, mortality among these patients was not directly related to hyponatraemia, but to other concomitant severe comorbidity. In study by Nzerue et al, mortality among patients with severe hyponatraemia was 20.2%.³ Papadakis et al had found that hyponatraemia is an independent risk factor for mortality in patients with cirrhosis.²⁶

CONCLUSION

Hyponatraemia is a common electrolyte abnormality found in hospitalised 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 co-morbidity was present in majority of patients and it predisposed the patients to hyponatraemia. Thiazides diuretics were the single most important aetiology of hyponatraemia. Treatment of hyponatraemia with hypertonic saline should be restricted to the patients with severe hyponatraemia and those with neurological symptoms of hyponatraemia treatment with

hypertonic saline is safe provided gradual correction of hyponatraemia is followed. Osmotic demyelination syndrome is a rare complication related to the treatment of hyponatraemia and should be suspected in a case of hyponatraemia who develop fresh neurological deficits while on treatment or after treatment with hypertonic saline. A systematic approach to the diagnosis of hyponatraemia with the application of simple diagnostic algorithms using history, clinical examination and laboratory findings to establish mechanism of hyponatraemia can significantly improve the assessment and management of hyponatraemia.

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