



## Hyponatremia in Critically ILL Patients: Assessment f Incidence, Etiology, Clinical Manifestations and Outcomes in ICU Setting

Authors

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### Abstract

*Hyponatremia is a common electrolyte disturbance occurring in critically ill patients. Mild hyponatremia (serum sodium, <135 mmol per liter) occurs in 15 to 22% of these patients and in approximately 7% of ambulatory patients; moderate hyponatremia (serum sodium, <130 mmol per liter) occurs in 1 to 7% of hospitalized patients. Symptoms range from nausea and malaise, with mild reduction in sodium, to lethargy, decreased level of consciousness, headache and if severe seizures and coma. Overt neurological symptoms most often are due to very low serum sodium levels usually <115 mEq/L, resulting in intracerebral osmotic fluid shifts, and brain edema. In patients with acute ST-elevation myocardial infarction, the presence of hyponatremia on admission or early development of hyponatremia is an independent predictor of 30-day mortality, and the prognosis worsens with the severity of hyponatremia. In our study Euvoletic was the most common type of Hyponatremia (55%) followed by Hypervolemic (25%) and Hypovolemic (20%). The most common cause of Hyponatremia was SIADH (34%) followed by Drugs (15%), Renal failure (12%), Heart failure (11%), Gastrointestinal losses (9%), Renal and Heart failure (9%), Endocrine disorders (4%), Chronic liver disease (4%), Burns (1%) and Cerebral salt wasting (1%). The mean ICU stay mild, moderate and severe Hyponatremia was 5.5±0.49 days, 5.1±0.38 days and 5.3±0.52 days respectively in our study.*

### Introduction

Hyponatremia is a common electrolyte disturbance occurring in critically ill patients. Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, seizures and coma. Hyponatremia is defined as a serum sodium concentration of <136mmol/l after the exclusion of “pseudo-hyponatremia” In most cases.<sup>1</sup> hyponatremia is mild and asymptomatic, but sometimes it is severe, with sodium concentrations less than 120 mmol/litre.

Severe hyponatremia is a serious medical condition, which is associated with substantial neurological complications and mortality.

Whereas hypernatremia always denotes hypertonicity, hyponatremia can be associated with low, normal, or high tonicity.<sup>2</sup>

A common clinical problem, hyponatremia frequently develops in hospitalized patients. A thorough understanding of etiology of hyponatremia is required to devise preventive as well as management measures.<sup>3</sup>

Mild hyponatremia (serum sodium, <135 mmol per liter) occurs in 15 to 22% of these patients and in approximately 7% of ambulatory patients; moderate hyponatremia (serum sodium, <130 mmol per liter) occurs in 1 to 7% of hospitalized patients.<sup>4</sup>

Hypoosmolality (serum osmolality <270 mOsm/kg) always indicates excess total body water relative to body solutes or excess water relative to solute in the extracellular fluid (ECF), as water moves freely between the intracellular compartment and the extracellular compartment. This imbalance can be due to solute depletion, solute dilution, or a combination of both.

Generally, hyponatremia is of clinical significance only when it reflects a drop in the serum osmolality (ie, hypotonic hyponatremia), which is measured directly via osmometry or is calculated as  $-2(\text{Na}) \text{ mEq/L} + \text{serum glucose (mg/dL)}/18 + \text{BUN (mg/dL)}/2.8$ .

The incidence of hyponatremia depends largely on the patient population and the criteria used to establish the diagnosis. A hospital incidence of 15-20% is common (defined as a serum sodium level of <136 mEq/L), while only 3-5% of patients who are hospitalized have a serum sodium level of less than 130 mEq/L. Hyponatremia's prevalence is lower in the ambulatory setting.

Severe hyponatremia (<120 mEq/L) has a high mortality rate; for instance, when the serum sodium level is less than 105 mEq/L, the mortality is over 50%, especially in alcoholics. In patients with acute ST-elevation myocardial infarction, the presence of hyponatremia on admission or early development of hyponatremia is an independent predictor of 30-day mortality, and the prognosis worsens with the severity of hyponatremia.<sup>5</sup>

The present perspective study was done at our tertiary care centre to assess the incidence of Hyponatremia with special emphasis on etiology in patients in Intensive Care Unit and to describe the clinical manifestations of hyponatremia in Intensive Care Unit patients.

### Aims and Objectives

1. To assess the incidence of hyponatremia in patients in Intensive care unit
2. To study the etiological factors, clinical manifestations and outcomes of hyponatremia in critically ill patients

### Materials and Methods

A Hospital Based prospective study of 100 patients admitted in Intensive Care Unit in MGM Hospital, Navi Mumbai over a period of 2 yrs.

#### Inclusion Criteria

Patients more than 18 years of age admitted in ICU with serum sodium level less than or equal to 135 mEq/L

#### Exclusion Criteria

Patients with age less than 18 years, Post-operative patients, Patients on renal replacement therapy, patients with hyperlipidemias, paraproteinemias (Pseudohyponatremia) and those receiving mannitol, radiographic contrast agents, or having hyperglycemia (translocational hyponatremia) were excluded from the study.

### Methodology

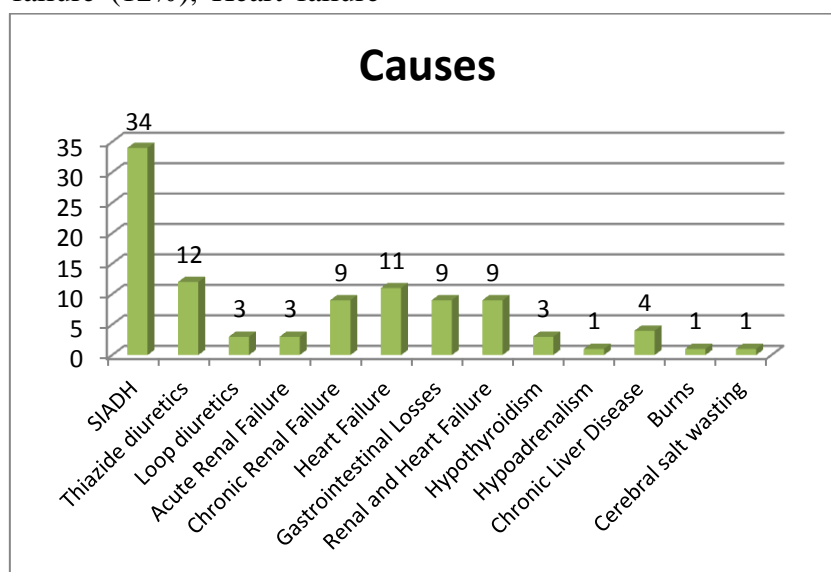
Institutional ethics committee clearance was taken. Detailed history including signs and symptoms present, coexistent diseases present like renal failure, HF, liver cirrhosis, subarachnoid haemorrhage, hypothyroidism, details of treatment received like thiazides and other drugs (SSRIs and carbamazepine), before admission to ICU and concomitant use of medications were recorded. For all patients these investigations were done- CBC, Sr. electrolytes, Sr glucose, renal function test, lipid profile, BUN, Sr Creatinine, Total proteins, Albumin to globulin ratio, TSH, urine electrolytes, osmolality and urine PH. Repeat evaluation of Sr electrolyte levels was done on subsequent days. Detailed examination including recording of vitals, general physical, systemic and neurologic examination was done. Treatment given, response to treatment and final outcome of the patient was recorded. Clinical evaluation of volume status was done for all patients. Parameters for critically ill patients in ICU including presence of acute renal failure, ventilator support with days, duration of ICU past and present and hospital days were recorded. Statistical analysis of data was done. Association among the study groups was assessed with the help of Fisher test, student 't' test and Chi-Square

test. 'p' value less than 0.05 were taken as significant.

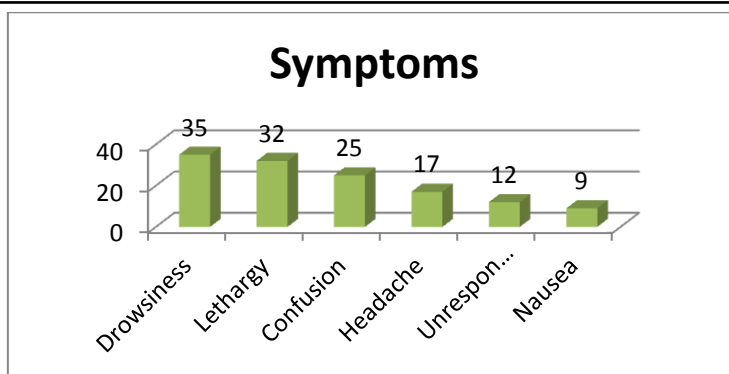
## Results

In our study Majority of the patients (25%) were from the age group of 61-70 years followed by 22% from the age group of 51-60 years, 18% from the age group of 41-50 years, 16% from the age group of 31-40 years, 10% from the age group of 21-30 years and 9% from the age group of >70 years. The mean age of patients was  $51.9 \pm 15.21$  years. 52% patients were male while female patients constituted 48% of the study group. 82% patients had hypertension while 55% and 28% had diabetes mellitus and ischemic heart disease respectively. 28% and 16% patients had renal failure and chronic liver disease respectively. The most common symptoms was drowsiness (35%) followed by lethargy (32%), confusion (25%), headache (17%), unresponsiveness (12%) and nausea (9%). Euvolemic was the most common type of Hyponatremia (55%) followed by Hypervolemic (25%) and Hypovolemic (20%). Cases were divided according to serum sodium level as mild (130-135 mEq/L), moderate (125-129 mEq/L) and severe (<125 mEq/L) Hyponatremia. The percentage of each group of Hyponatremia was 65%, 15% and 20% respectively. The most common cause of Hyponatremia was SIADH (34%) followed by Drugs (15%), Renal failure (12%), Heart failure

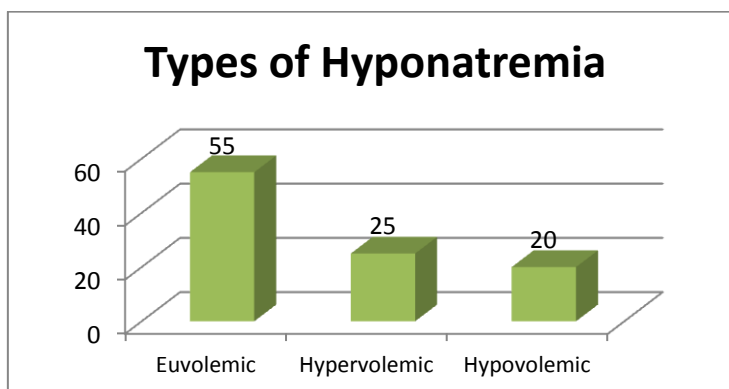
(11%), Gastrointestinal losses (9%), Renal and Heart failure (9%), Endocrine disorders (4%), Chronic liver disease (4%), Burns (1%) and Cerebral salt wasting (1%). The mean ICU stay mild, moderate and severe Hyponatremia was  $5.5 \pm 0.49$  days,  $5.1 \pm 0.38$  days and  $5.3 \pm 0.52$  days respectively. There was no significant association between severity of Hyponatremia and mean ICU stay as per Student t-test. It was observed that 90% patients improved while 10% patients in our study died. Deaths with Hyponatremia were not uniform in each age group but more common in the age group of 61-70 years. There was significant association of age and outcome ( $p=0.025$ ). There was comparable death of male and female patients (6% vs. 4%). There was no significant association of gender and outcome ( $p=0.593$ ). Patients with Ischemic heart disease and renal failure were significantly associated with death. There was significant association of comorbidities and outcome. Hypervolemic and Hypovolemic hyponatremia was associated with mortality and this association was statistically significant as per Student t-test ( $p=0.002$ ). Among the patients who died, mild, moderate and severe hyponatremia was present in 5 (5%), 3 (3%) and 2 (2%) patients respectively. However statistical significance could not be reached between severity of hyponatremia and mortality in our study.



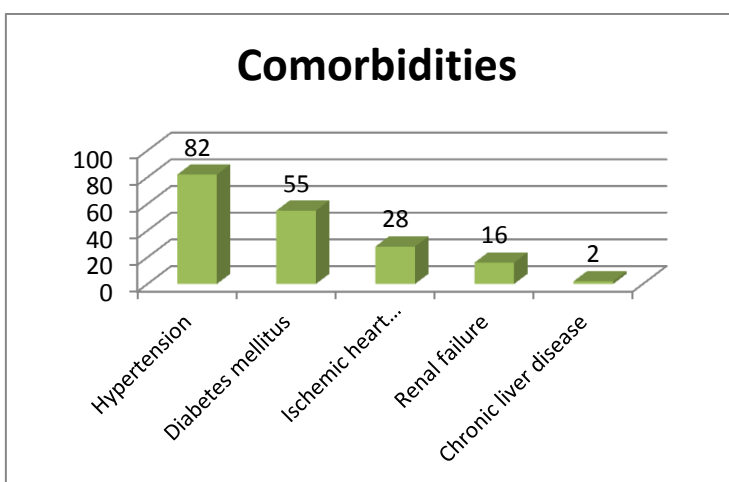
**Graph 1:** Distribution of patients according to Causes of Hyponatremia



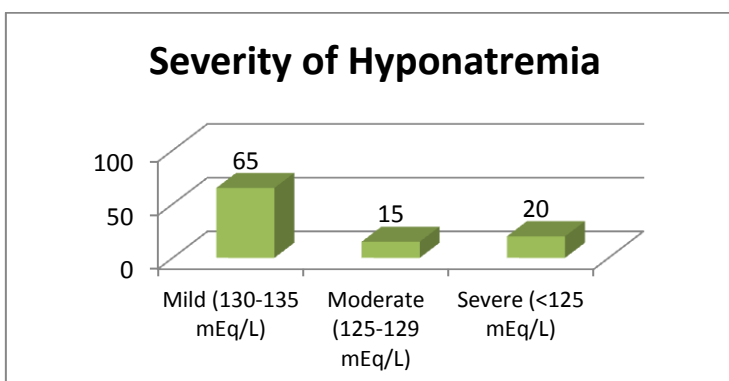
**Graph 2:** Distribution of patients according to Symptoms



**Graph 3:** Distribution of patients according to Types of Hyponatremia

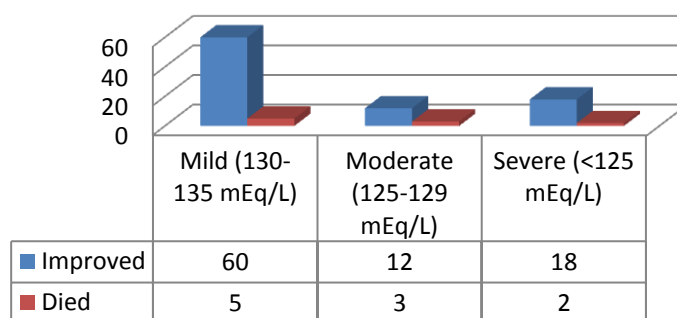


**Graph 4:** Distribution of patients according to Comorbidities



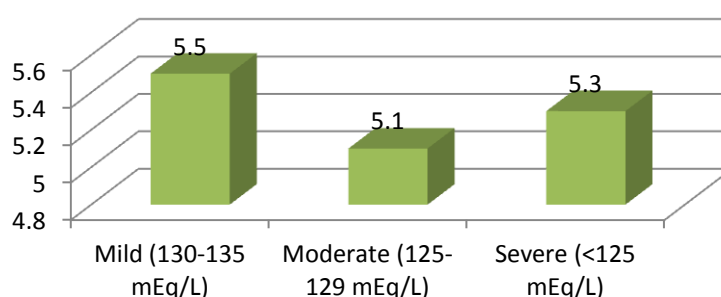
**Graph 5:** Distribution of patients according to Severity of Hyponatremia

### Association of Severity of Hyponatremia and Outcome



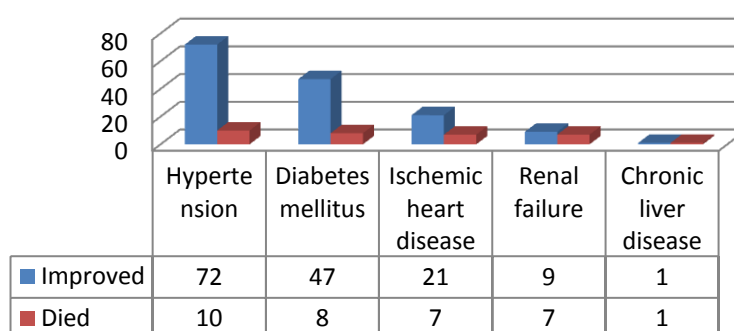
**Graph 6:** Association of Severity of Hyponatremia and Outcome

### ICU Stay (days)

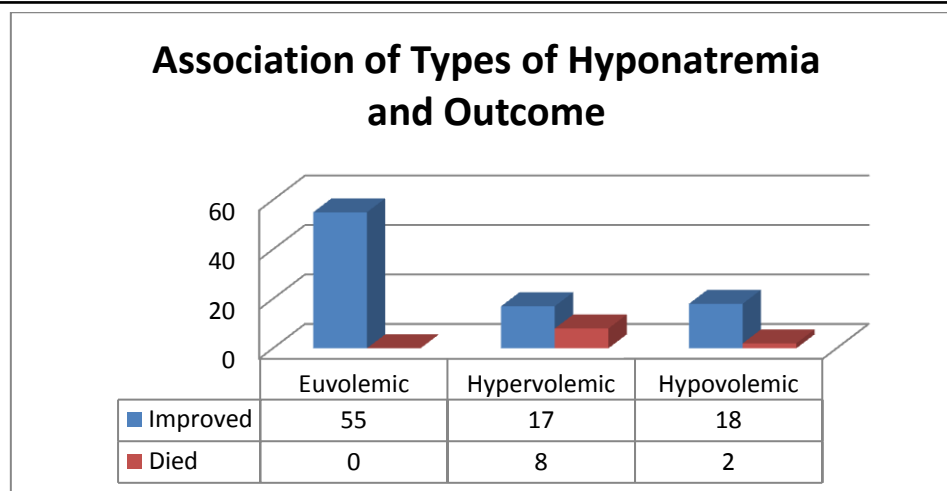


**Graph 7:** Association of Severity of Hyponatremia and mean ICU stay

### Association of Comorbidities and Outcome



**Graph 8:** Association of Comorbidities and Outcome



**Graph 9:** Association of Types of Hyponatremia and Outcome

### Discussion

Hyponatremia is the most common electrolyte disorder in hospitalized patients. Hyponatremia is important to recognize because of the potential morbidity, mortality, and the economic impact on the patient and the health care.

Symptoms range from nausea and malaise, with mild reduction in sodium, to lethargy, decreased level of consciousness, headache and if severe seizures and coma. Overt neurological symptoms most often are due to very low serum sodium levels usually  $<115$  mEq/L, resulting in intracerebral osmotic fluid shifts, and brain edema.

Increased intracranial space due to naturally occurring age related brain atrophy is known to play an important role in brain adaptation to hyponatremia. The finding suggests that even in the presence of cerebral edema, if the brain is able to swell without generating a significant increase of intracranial pressure, the prospects for patient survival may be substantially improved<sup>9</sup>. Studies have shown that both aging and male gender confers protection against hyponatremia induced seizures, although the reasons are unclear.<sup>10</sup>

The most common symptoms in our study was drowsiness (35%) followed by lethargy (32%), confusion (25%), headache (17%), unresponsiveness (12%) and nausea (9%).

Patgiri PR et al<sup>7</sup> observational study on incidence, clinical profile, etiology and comorbidities associated with hyponatremia reported mean

sodium level on admission was 120.83 mEq/L and after correction was 129.54 mEq/L. Drowsiness (35%), irrelevant talk (25%), headache (17%) and unresponsiveness (12%) were the common presenting symptoms. patients also presented with other symptoms such as chest pain, abdomen pain, decreased appetite which could not be accounted for by hyponatremia.

It was observed in the current study that Euvolemic was the most common type of Hyponatremia (55%) followed by Hypervolemic (25%) and Hypovolemic (20%).

Patgiri PR et al<sup>7</sup> observational study on incidence, clinical profile, etiology and comorbidities associated with hyponatremia found 80% were euvolemic, 12% were overloaded and 8% dehydrated.

In our study, cases were divided according to serum sodium level as mild (130-135 mEq/L), moderate (125-129 mEq/L) and severe ( $<125$  mEq/L) Hyponatremia. The percentage of each group of Hyponatremia was 65%, 15% and 20% respectively.

Patil S et al<sup>8</sup> Cross-sectional prospective observational study on incidence, etiological factors, clinical manifestations and treatment modalities for hyponatremia in ICU patients reported serum osmolality in patients suffering from severe hyponatremia were  $246.63 \pm 41.57$ , and mild to moderate were  $278.59 \pm 12.3$ , and the  $P < 0.001$ .



Glucose being an osmotically active molecule, hyperglycemia can induce a fall in serum sodium levels by shifting water from intra-cellular to extra-cellular compartments. It has been calculated that serum sodium falls by 1.6 to 2.4 mmol/L for every 5 mmol/L rise in serum glucose levels<sup>11</sup>. Hyponatremic hypertensive syndrome is a well-known entity, the most common association being in patients with essential hypertension receiving diuretics.<sup>6</sup>

The most common cause of Hyponatremia in our study was SIADH (34%) followed by Drugs (15%), Renal failure (12%), Heart failure (11%), Gastrointestinal losses (9%), Renal and Heart failure (9%), Endocrine disorders (4%), Chronic liver disease (4%), Burns(1%) and Cerebral salt wasting (1%).

Patil S et al<sup>8</sup> cross-sectional prospective observational study on incidence, etiological factors, clinical manifestations and treatment modalities for hyponatremia in ICU patients reported 34% of the patients were asymptomatic, and 66% had abnormal behavior. There was a wide range of etiologies, most common being cerebral malaria (15%), sepsis (13%), pneumonia (14%), hypothyroidism (12%), syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (8%), diuretics (9%), heart failure (8%), renal failure (7%), liver disorder (7%), and vomiting (5%).

Patgiri PR et al<sup>7</sup> observational study on incidence, clinical profile, etiology and comorbidities associated with hyponatremia reported common causes of hyponatremia were SIADH (30%) followed by Drugs (24%). Among the types of diuretics used hydrochlorothiazide was used by 83%, frusemide by 10% and chlorthalidone by 7%. None of the subjects were on diuretics when SIADH was causing hyponatremia. Mannitol (6%) and Cisplatin (5%) were the other drugs found to be associated with drug induced hyponatremia.

Hyponatremia did not appear to have any significant effect on the duration of ICU stay. Chua M et al<sup>14</sup> and Gill G et al<sup>12</sup> studies on implications of hyponatremia in elderly

hospitalized patients have independently shown that the drop in hyponatremia had a greater effect than the severity of hyponatremia on length of stay in hospital, mortality & institutionalization.

It was observed in our study that among the patients who died, mild, moderate and severe hyponatremia was present in 5 (5%), 3 (3%) and 2 (2%) patients respectively. There was no significant association of severity of hyponatremia and Outcome as per Student t-test ( $p=0.358$ ).

Patil S et al<sup>8</sup> cross-sectional prospective observational study on incidence, etiological factors, clinical manifestations and treatment modalities for hyponatremia in ICU patients reported mortality level based on serum sodium level. In less than 120 serum sodium the percentage of mortality was 16.6% while in more than 125 it was 27.3%. Overall mortality rates during the treatment of hyponatremia were 57% in 0.9% isotonic solution infusion in which death was 14.04%. In treatment with fluid restriction was around 9.76% death, in demeclocycline was 18.75%, in hypertonic solutions (3% or 5%) was 18.18%, in salt tablets it was found 14.29%, in furosemide it was around 20.00%, and in vasopressin receptor antagonist.

Reynolds RM et al<sup>13</sup> study on disorders of sodium balance studies in the past indicated a higher mortality in the elderly patients with severe hyponatremia, with mortality ranging from 33% to 86%.

Treatment of hyponatremia with hypertonic saline should be restricted to the 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 and 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 using history, clinical examination, and laboratory findings to establish the mechanism of hyponatremia can significantly improve the assessment and management of hyponatremia.

## References

1. Horacio J, Adrogué MD, Andnicolaos E, Madias MD. The New England Journal of Medicine review article Volume 342 Number 21 may 2000.
2. Kennedy PG, Mitchell DM, Hoff brand BI. Severe hyponatremia in hospital inpatients. *BMJ* 1978;2:1251-1253,
3. Anderson RJ. Hospital-associated hyponatremia. *Kidney Int* 1986; 29:1237-47.
4. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *American Journal of Medicine* 2006;119:Suppl 1:S30-S35.
5. Hypoosmolar states — hyponatremia. In: Rose BD. *Clinical physiology of acid-base and electrolyte disorders*. 4th ed. New York: McGraw-Hill, 1994:651-94.
6. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. *Am J Med*. 1999;106:399–403.
7. Patgiri PR, Biswas TK, Sabnis S, Damle S. Study of Clinical Symptoms and Etiology of Hyponatremia in Elderly in Intensive Care Unit. *JMSCR* 2016;4( 11): 13917-13922.
8. Patil S, Mukherji A, Shetty A. Incidence of Hyponatremia in Critically Ill Patients in Intensive Care Unit: Observational Study. *Int J Dent Med Spec* 2016;3(1):12-15.
9. Rao MY, Sudhir U, Anil Kumar T, Saravanan S, Mahesh E, Punith K. “Hospital-Based Descriptive Study of Symptomatic Hyponatremia in Elderly Patients”
10. Arieff AI, Kucharczyk J, Ayus JC, et al. “Age, gender and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy”. *Am J Physiol* 1995;268:143-1152.
11. Dzau VJ, Packer M, Lilly LS, et al. “Prostaglandins in severe congestive heart failure. Relation to activation of the renin-angiotensin system and hyponatremia.” *N Engl J Med* 1984; 310:347.
12. Gill G, Bobby Huda, Alice Boyd, Karolina Skagen, David Wile, Ian Watson, Charles Van Heyningen. “Characteristics and mortality of severe hyponatremia – a hospital based study.” *Journal of Clinical Endocrinology* 2006; 65 (2).
13. Reynolds RM, Padfield PL, Seckl JR. “Disorders of sodium balance.” *BMJ* 2006;332:702-5.
14. Chua M, Graeme E. Hoyle, Roy L Sozia. “Prognostic implications of hyponatremia in elderly hospitalized patients.” [*Archive of Gerontology & Geriatrics*. 2007; Vol45:3.