A STUDY ON CLINICAL PROFILE OF EUVOLEMIC HYPONATREMIA IN ELDERLY HOSPITALISED PATIENTS

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled **"A STUDY ON CLINICAL PROFILE OF EUVOLEMIC HYPONATREMIA IN ELDERLY HOSPITALISED PATIENTS"** is the bonafide work of **DR.MINY SUSAN ABRAHAM,** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine, Branch I** examination to be held in **April 2017.**

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DECLARATION

I**, DR.MINY SUSAN ABRAHAM**, solemnly declare that this dissertation titled **"A STUDY ON CLINICAL PROFILE OF EUVOLEMIC HYPONATREMIA IN ELDERLY HOSPITALISED PATIENTS"**is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.R.PRABHAKARAN.M.D,** Professor, Department of General Medicine , Madurai Medical college , Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **April 2017.**

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INTRODUCTION

Hyponatremia is defined as plasma sodium concentration < 135 meq/1. It is a very common disorder occurring in about 22% of hospitalized patients.

It can be classified on the basis of serum osmolality into hypertonic, isotonic and hypotonic type. Hypotonic hyponatremia is further classified into hypervolemic, euvolemic and hypovolemic.

Mild hyponatraemia is generally asymptomatic, but where the decrease in serum sodium is marked (<125 mmol/1) or acute (occurring over <48 h), serious neurological complications can occur as a result of cerebral oedema. Early symptoms of headache, muscular weakness, nausea, lethargy, ataxia and confusion can progress to seizures, irreversible neurological damage, coma and death, if unrecognized and untreated. In chronic hyponatraemia, cerebral wasting of intracellular potassium followed by organic osmolytes reduces cerebral swelling, delaying the onset of symptoms. The correction of hyponatraemia should be carefully managed, because of its association with the osmotic demyelination syndrome (central pontinemyelinolysis). Patients with chronic hyponatraemia appear to be particularly vulnerable to this complication.

Severe hyponatraemia has a high mortality. In order to give correct treatment, an accurate clinical assessment must be made, focusing on fluid status, chronicity and potential aetiology, along with appropriate investigations.

Hyponatremia is common among hospitalized patients and can lead to serious

complications, but its assessment is challenging and strategies for its management have traditionally been suboptimal. New therapies are emerging that promise a more targeted approach to regulating body water and sodium balance in patients with this disorder.

Hyponatremia is especially common in older people. The incidence is muchmore in elderly mainly owing to impaired ability to maintain water and electrolyte homeostasis in response to diet, drugs and environmental changes. Several changes in the mechanisms that regulate water and sodium balance occur as a normal part of the aging process, such as decreased glomerular filtration rate, decreased renal bloodflow, impaired ability to dilute urine, and impaired water excretion. These physiologic changes result in an increased likelihood of developing hyponatremia with increasing age. Recent evidence highlights that even mild, chronic hyponatremia can lead to cognitive impairment, falls and fractures, the latter being in part due to bone demineralization and reduced bone quality. Hyponatremia is therefore of special significance in frail older people. Management of hyponatremia in elderly individuals is particularly challenging. The underlying cause is often multi-factorial, a clearhistory may be difficult to obtain and clinical examination is unreliable. Established treatment modalities are often ineffective and carry considerable risks, especially ifthe diagnosis of underlying causes is incorrect.

OBJECTIVES

1. To study clinical features of euvolemic hyponatremia in elderly hospitalized subjects.

2. To study etiology of euvolemic hyponatremia in elderly hospitalized subjects.

3. To assess the morbidity and mortality due to hyponatremia.

BACKGROUND

Hyponatremia

Hyponatraemia is an electrolyte abnormality commonly encountered in clinical practice with a daily incidence and prevalence rates of 0.98% and 2.43% respectively. Hyponatremia means an excess of body water when comparing with body's sodium content and is frequently defined as a serum sodium concentration of less than 135 mEq/L. The incidence of hyponatremia varies depending upon the underlying conditions and the criteria used to define it. When defined as a serum sodium concentration of less than 135 mEq/1 hyponatremia is being described in 15% to 22% of hospitalized patients. In studies defining it as a concentration of 130mEq/L or less, the incidence of hyponatremia is 1% to 4%.

It is also associated with 60-fold increase in morbidity and mortality compared with patients without any evidence of hyponatraemia. Most cases of hyponatraemia arises out of water imbalance rather than sodium imbalance. The aetiology of most cases of hyponatraemia can be diagnosed from the history, physical examination and simple laboratory tests. As aggressive or inappropriate management of hyponatraemia proved to be more harmful than the condition itself, clinicians should be familiar with the diagnosis and management of various forms of hyponatraemia.

Basic principles of sodium balance

Plasma sodium concentrations normally average 140 mEq/1 or

140mmol/l.Sodium is the principal osmole, determinant in maintaining extracellular fluid (ECF) volume and in the regulation of blood pressure and osmotic equilibrium. Sodium is also the principal regulatory osmole of the effective circulating volume (ECV), that is, the arterial blood volume perfusing the tissues.

The ECF sodium is maintained by the action of Na^+/K^+-ATPase.Water can freely cross cell membranes to maintain isotonicity between the intracellular fluid (ICF) and ECF, but sodium cannot freely cross and requires energy dependent pumps to be transported across the cell membranes.

The plasma sodium concentration is dependent on multiple factors including sodium intake, osmolality and tonicity of plasma, the renin angiotensin system

(RAA), total body potassium and water. The following equation depicts therelationship between plasma Na^+ concentration and the total body content of sodium,potassium and water (TBW).

$$\text{Plasma } Na^+ = \frac{Totaldody Na^+ \; Totalbody K^+}{Total\ body\ water}$$

The primary determinant of plasma osmalility is the concentration of sodium salts with minor contributions from glucose and blood urea nitrogen (BUN). Plasma osmolality = (2 x $[Na^+]$) + ([glucose]/18) + ({BUN}/2.8)

The $[Na^+]$ is multiplied by two to account for the accompanying anions

(mostly chloride and bicarbonate) that provide electrical neutrality.

The corrections are made in the glucose concentration and BUN to convert mg/dl into mmol/1. As urea is lipid-soluble and equilibrates across the cell membranes, it is an ineffective osmole and does not contribute to fluid distribution, and therefore it is omitted from calculation of effective plasma osmolality as follows:[14]

Effective plasma osmolality = (2x [Na^+]) + ([glucose]/! 8).Normal plasma osmolality varies between 280 and 290mOsm/l. A discrepancy between the measured and calculated osmolality is referred to as an osmolal gap.A high concentration of osmotically active molecules in plasma such as ethanol, mannitol, methanol, ethylene glycol or isopropyl alcohol.leads to significant osmolal gap.

Average sodium intake is 4-5 g/day (173-217 mmol/day). Sodium chloride is table salt, which dissolves in water to give sodium and chloride ions. Sodium is 0.39 weight of sodium chloride. So 1 g of table salt or salt tablets contains approximately 400 mg of sodium. One teaspoon of table salt contains about 6 g of NaCl with approximately 2.4 g (104mmol) sodium. One gram of sodium yields 43 mEq of sodium ions, whereas 1 g of sodium chloride yields 17 mEq of sodium ions.

The total amount of filtered sodium load (25,200 mmol or 583 g/day) is the product of the glomerular filtration rate (GFR) (1801/day) and plasma sodium

concentrations (140 mmol/1). Therefore, to maintain sodium balance with a dietary intake of approximately 200 mmol or 3.2 g/day, a total of 25,000 mmol (i.e. 99.6% of the filtered load) must be reabsorbed.

Proximal tubule reabsorbs about 60-70% of the filtered sodium . Ascending limb of the loop of Henle reabsorbs an additional 20-30%. The majority of the remaining sodium (5-10%) is reabsorbed in the distal tubule and collecting duct, under the regulation of aldosterone.

Sudden decrease in blood volume is sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch and renal afferent arterioles leading to activation of the RAA system, stimulation of thirst and non osmotic release of arginine vasopressin. Juxtaglomerular cells of the kidney synthesize and secretes renin. Renin isoenzymes have been found in many tissues, including brain, adrenals, vascular beds, uterus and placenta,eventhough renin is mainly produced by the kidneys

Renin cleaves its substrate angiotensinogen to generate the angiotensin I, which is converted to angiotensin II by angiotensin I-converting enzyme. Angiotensin II stimulates aldosterone secretion through the adrenal cortex and also partially suppresses renin secretion by a direct effect on the juxtaglomerular cells. Aldosterone increases sodium reabsorption and potassium excretion in the distal tubule and the collecting duct of the nephron; the site where ADH controls the rate of water reabsorption also.

Tonicity refers to the effect of a solution on the cell volume. An isotonic solution doesn't have any effect on cell volume, whereas hypotonic and hypertonic solutions increase and decrease cell volume respectively. Infusion of isotonic saline causes volume expansion without changing the plasma osmolality. And the steady state is restored by renal sodium excretion,ADH release and thirst are not altered. On the other hand, intake of large quantities of NaCl without water (e.g. consumption of salted pretzels, potato chips or peanuts) results in an elevation in the plasma osmolality and stimulation of thirst and ADH secretion leading to ECV expansion. ECF volume expansion will suppress the RAA system, resulting in increased urinary sodium excretion.Thus, the maintenance of the ECV is dependent on the regulation of sodium balance, while plasma osmolality is largely maintained by the regulation of water balance.

Aging increases likelihood of hyponatremia

Several physiologicalchanges occur in the regulation of water and sodium balance as a part of the normal aging process, such as decreased glomerular filtration rate, decreased renal blood flow, impaired ability to dilute urine, and impaired water excretion. These changes result in an increased likelihood of developing hyponatremia with increasing age.

older persons are susceptible to stresses on water balance because of the age related decrease in total body water (relative and absolute). Average healthy 30- to 40-year-old persons have a total-body water content of 55 to 60 percent. By age 75 to 80 years, the total-body water content has declined to 50 percent, with even more of a decline in elderly women.Factors resulting in the increased susceptibility to various hemodynamic changes are decreased baroreceptor reflexes, less arterial distensibility,, sluggish homeostatic mechanisms. After ingestion of water the body fluid compartments are diluted. With less than 1% decrease in osmolality, the hypothalamus- pituitary axis responds by inhibiting ADH release. In the absence of ADH, the kidney excretes dilute urine. However in the presence of inappropriately elevated ADH a relative water excess can result in hyponatremia.

The thirst mechanism decreases as, age advances which significantly

impairs the capacity to maintain homeostasis thereby intensifying the risk for dehydration. The dimunition in thirst is being attributed in part to a defect in an opiod mediated thirst center in CNS..Maximal urinary concentrating capacity also diminishes with age which also intensifies the risk for dehydration. Eventhough ADH release donot have an association with ageing ,there occurs a failure of the normal response of kidney to ADH,as indicated by the increased level of ADH for any given plasma osmolality.

The neurohumoral mechanism of fluid and electrolyte balance depends upon an intricate interaction between aldosterone, ADH and ANP. Alterations in these hormonal levels are partly responsible for the changes in fluid balance with aging. Younger individuals exhibit a diurnal variation for the ADH release with increased secretion occurring at night.

In elderly these diurnal variations are absent. On comparing with younger individuals the levels of ADH are increased for any given plasma osmolality.The proposed mechanism for these exaggerated ADH response is osmoreceptor hypersensitivity. In the aged there is a five fold increase in ANP concentration over the basal levels. Increased ANP leads to direct suppression of renin with a secondary decrease in angiotensin II and in aldosterone, resulting in renal loss of sodium associated with ageing.

In elderly the capacity for excreting a water load is delayed.. This propensity may contribute to the frequently observed episodes of hyponatremia

in hospitalized elderly patients who are receiving hypotonic intravenous fluids or whose fluid intake is not properly monitored.

Other changes in renal physiology and anatomy that increase the elderly patient's susceptibility to alterations of water imbalance include decreased renal mass, cortical blood flow and glomerular filtration rate, as well as impaired responsiveness to sodium balance.

Accurate appreciation of the etiology of hyponatremia is essential, not only for appropriate clinical management but also to prevent development of hyponatremia. At present, there are few quality studies reporting etiology of hyponatremia in older people. Most reports are from retrospective studies that rely on diagnosis made by non-expert clinicians retrospectively reviewing case notes, which frequently lack sufficient detail to allow accurate diagnosis. The reported commonest cause of hyponatremia is SIADH. However, with the increased prevalence of hyponatremia in older people there is no corresponding increased prevalence of SIADH. This raises concern that SIADH may be over diagnosed, particularly in hypovolemic older people. The etiology of hyponatremia in older people is predominantly multifactorial, with patients presenting with doubtful signs of hydration.

Common underlying causes of hyponatremia include drugs (thiazide and loop diuretics, antidepressants, anticonvulsants, non-steroidal anti-inflammatories, proton pump inhibitors), co-morbidities (congestive cardiac

failure, renal failure, cirrhosis, respiratory infections), fluid overload and volume depletion.

The impact of a lifetime of accumulated disease and comorbidities must also be duly considered in every clinical situation with an elderly patient, in addition to age-related physiologic changes. The elderly patient has a diminished reserve of water balance and an impaired regulatory mechanism. Thirst sensation, concentrating abilities and hormonal modulators of salt and water balance are sluggish and highly susceptible to being overtaken by morbid or iatrogenic events.

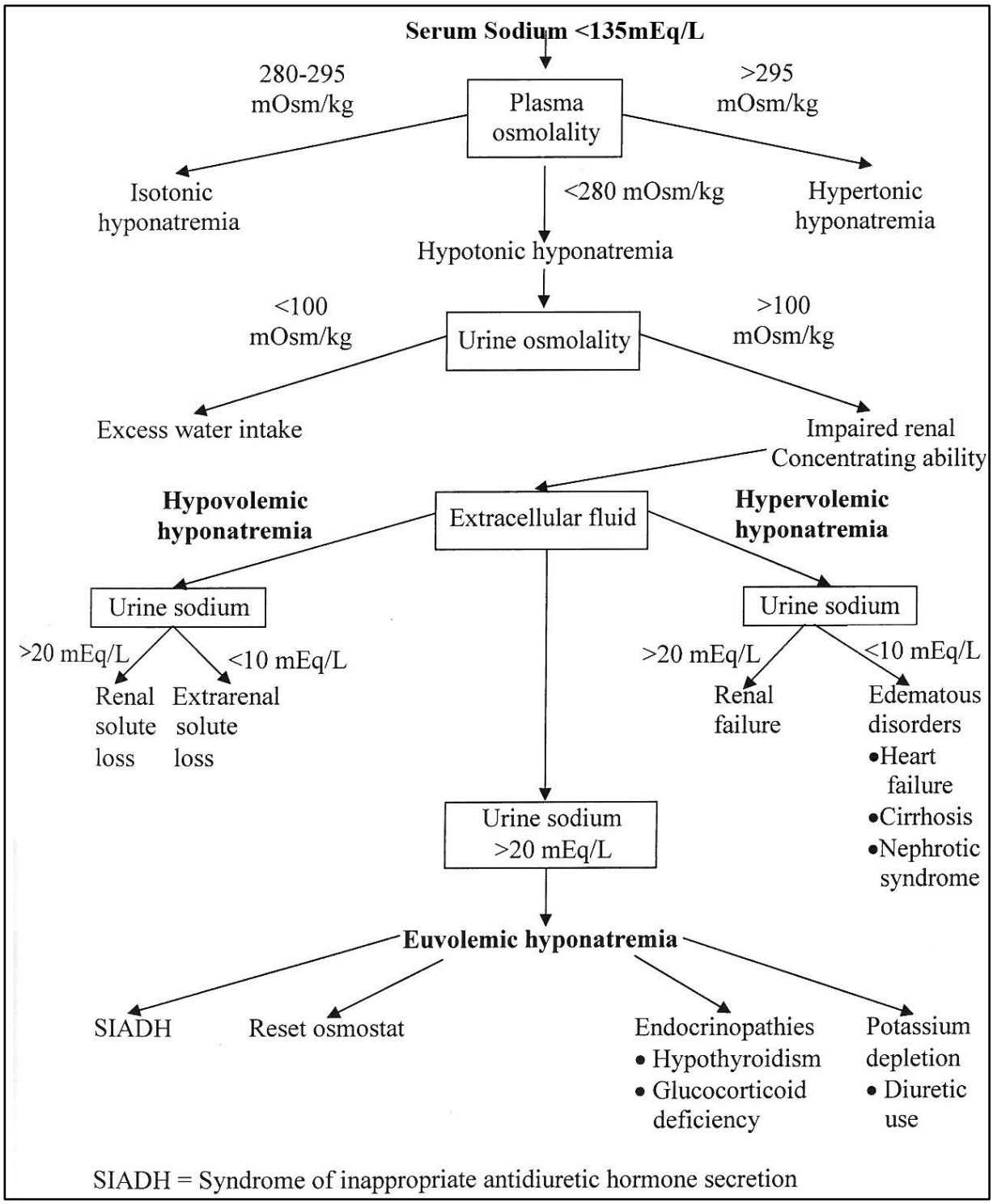
Classification of hyponatraemic disorders

Hyponatraemia is defined as a plasma sodium concentration less than135 mEq/1.[13] Chan ges in plasma sodium are typically inversely proportional to the total body water. In most cases, hyponatraemia is the result of retention of more water in relation to sodium and potassium with a possible concurrent abnormality in sodium balance. The appropriate physiological response to hyponatraemia is suppressed ADH release that in turn facilitates the excretion of the excess water to restore the normal sodium and water homeostasis. In the absence of advanced renal disease limiting water excretion or a massive increase in water intake that exceeds water excretory capacity, hyponatraemia is almost always because of an inability to suppress ADH.

To identify the aetiology of hyponatraemia, a systematic algorithm that is

based on the measurements of plasma osmolality and an estimation of the volume of the total body water should be followed. It is noteworthy that in any given patient, multiple aetiologies may contribute to the pathogenesis of hyponatraemia. For example, the patient with congestive heart failure (CHF) who has ADH secreting lung cancer and develops severe hyperglycaemia would have at least three independent causes of hyponatraemia. To facilitate the differential diagnosis, the first step in the evaluation of hyponatraemia irrespective of the volume status should start by measuring the plasma osmolality. On the basis of the osmolality, hyponatraemia is classified as isotonic, hypertonic and hypotonic.

Figure 1: Algorithm for classifying hyponatremia



Isotonic hyponatraemia

Isotonic hyponatraemia can be produced by the addition of an isosmotic, non-sodium substance to the ECF. It can happen with the use of non-conductive flushing solutions that contain glycine or sorbital during transurethral resection of the prostate (TURP), bladder irrigation and during laparoscopic surgery and hysteroscopy in women. ' Variable quantities of these solutions can be absorbed via the prostatic veins. The plasma osmolality changes over time and can be either near normal or low. Glycine initially acts as an ineffective osmole (similar to urea), raising the plasma osmolality without affecting water distribution between the fluid compartments. Osmolal gap is also increased because of the excess organic solute. However, when glycine enters the ICF compartment, the free water left behind in the ECF can result in symptomatic dilutionalhyponatraemia, that is referred to sometimes as the TURP syndrome.

In patients with normal renal function, metabolism and excretion of the excess solute will rapidly correct the hyponatraemia. Hypertonic saline can be given if the plasma osmolality is reduced, but may not be effective in patients with normal plasma osmolality. In symptomatic patients with relatively normal plasma osmolality and in patients with end-stage renal disease, haemodialysis will correct the hyponatraemia and remove glycine and its toxic metabolites.

Pseudohyponatraemia is seen when the sodium concentrations are measured by Flame photometry that determines sodium content per litre of

plasma. In normal subjects, each litre of plasma contains about 930 ml of water (93%) with fats and proteins accounting for the remaining 70 ml (7%). Thus, a normal plasma sodium concentration of 140mEq/l represents a concentration in the plasma water of 150 mEq/1 as calculated in the following equation.

140 mEq/1 plasma + 0.93 litre of water plasma

Per litre of plasma = 150 mEq/1 plasma water

In patients with marked hyperproteinemia greater than lOg/dl, the plasmawater fraction may fall as low as 720 ml/1 (< 80%). Plasma osmolality remainsisotonic, because lipids and proteins do not substantially affect osmolalitymeasurement. In these patients when sodium is measured per litre of plasma, thereported sodium concentration will be artificially reduced as the specimen containsless plasma water.

Table 1: The comparative profile of the laboratory features of various conditions of altered plasma tonicity

Condition	Measured plasma Na	Measured plasma osmolality	Effective plasma osmolality
True hypotonicity	Decreased	Decreased	Decreased
Increased non-sodium 1 XF solutes			
Hyperglycaemia	Decreased	Increased	Increased
Mannitol administration	Decreased	Increased	Increased

Glycine, Sorbital	Decreased	Variable	Normal
Laboratory artifact			
Hyperlipidaemia	Decreased	Normal	Normal
Hyperproteinemia	Decreased	Normal	Normal
Gamma-globulins	Decreased	Normal	Normal

This laboratory artefact of pseudohyponatraemia can be eliminated by the direct measurement of serum sodium using ion-selective electrodes (ISE).

Hyperlipidaemia interferes with ISE as well as now rarely used flame photometry measurements. Some interference is seen when triglycerides are >10 mmol/1, and when triglycerides are > 20 mmol/1 a significant interference in the measurement occurs. Laboratories use reagents such as Lipoclear to address this issue, but the results need adjusting for volume changes and errors can occur in these adjustments.

Hypertonic hyponatraemia

Hypertonic hyponatraemia occurs with hyperglycaemia and mannitol administration. Glucose and mannitolosmotically pull intracellular water into the extracellular space, which dilutes all the ECF electrolytes resulting in hyponatraemia. When evaluating hyponatraemia in the presence of hyperglycaemia, the corrected sodium concentration should be calculated. The sodium concentration falls 1.6mEq/l for every lOOmg/dl (5.5 mmol/1) rise in

glucose when the glucose concentration is between 100 (5.5 mmol/1) and 400mg/dl (22 mmol/1). If the initial glucose concentration is above 400 mg/dl (> 22 mmol/1), the sodium concentration falls 2.4 mEq/1 for every 100 mg/dl (5.5 mmol/1) rise in glucose. As this calculation corrects sodium only and no other ECF electrolytes (K^+, *C*\~ and $HC03^-$), anion gap should not be calculated using the corrected sodium value. Hypertonic hyponatraemia is not considered pseudohyponatraemia because it is not an artefact of sodium measurement.

Hypotonic hyponatraemia

As sodium is the predominant extracellular osmole, most cases of hyponatraemia are hypotonic and can be further classified based on the patient's volume status as (i) hyponatraemia with contracted ECF volume (hypovolaemia); (ii) hyponatraemia with expanded ECF volume (hypervolaemia); and (iii) hyponatraemia with normal ECF volume (euvolaemia). For a diagnosis of hypotonic hyponatraemia, the effective osmolality must be < 275 mOsm/kg of water.

Hypovolaemic-hypotonic hyponatraemia

Depletional hyponatraemia results from decreased sodium intake or increased losses of sodium, contraction of ECF and appropriate increase in ADH secretion with subsequent free water retention. It is often accompanied by the physical findings of extracellular volume deficit such as flat neck veins, decreased skin turgor, dry mucous membranes, orthostatic hypotension and

tachycardia.

Examination of the urinary Na^+ concentration is helpful in assessing whether losses are renal/extra renal in origin. Urinary Na^+ concentration of <20 mEq/1 reflects a normal renal response to volume depletion and points to an extra renal source of Na^+ loss. In patients with hypovolaemic hyponatraemia, urinary Na^+ concentration in excess of 20 mEq/1 points to the kidney as the source of the fluid and Na^+ losses.

Hypovolaemic hyponatraemia can be aggravated when fluid losses are replaced with hypotonic fluids. When isotonic saline is used, it eliminates the stimulus for ADH release, thereby allowing the excess water to be excreted. This effect may normalise the plasma sodium concentration rapidly and may be undesirable in patients with chronic hyponatraemia (> 48 h). Administration of desmopressin or hypotonic solutions may be helpful to slow the rate of sodium correction in these patients.

Although there are many causes of hypovolaemic-hypotonic hyponatraemia, the two common aetiologies are diuretic induced and cerebral salt wasting (CSW).

Table 2: Causes of depletional **hyponatremia**

GI losses	Vomiting
	Diarrhoea

	Fistulas
	Gastrointestinal suction or drainage tubes
Third spacing of fluids	Burns
	Peritonitis
	Bowel obstruction
	Pancreatitis
Renal losses	Adrenal insufficiency
	Proximal renal tubular acidosis - sodium losses induced by bicarbonaturia
	Salt-wasting nephropathy (interstitial nephropathy, medullary cystic disease, polycystic kidney disease)
	Presence of an osmotically active non-reabsorbable solute in the urine (glycosuria, ketonuria, mannitol, urea) causes renal excretion of sodium
	Severe vomiting with the metabolic alkalosis and bicarbonaturia - sodium accompanies bicarbonate in the urine to maintain electroneutrality.
	Cerebral salt wasting
	Diuretic use
Sweat losses	Marathon runners

Diuretics are commonly used in the management of hypertension and CHF. A subset of diuretics, especially thiazide containing preparations such as the amiloride/ hydrochlorthiazide combination pills, causes significant hyponatraemia. ' A similar risk is associated with the use of some antibiotics that contribute to the high incidence of hyponatraemia in intensive care units.

Hyponatraemia is a potentially fatal complication of thiazide therapy, even when low doses (12.5-25 mg/day) are used. It is usually evident within 14 days ofonset of therapy, but can occur up to 2 years later. It appears to be more common in women and elderly patients with low body weight with an underlying tendency of increased water intake. While the initial volume depletion induced by thiazides can stimulate the release of ADH, susceptible patients appear to have a reduced innate ability to excrete water load. These patients may not have clinical features of volume depletion described above and can be also classified as euvolaemic hypotonic hyponatraemia. Cerebral oedema is extremely rare even when plasma sodium concentration is 115 mEq/1. In many of these patients, hyponatraemia is reproducible with a thiazide rechallenge.

The use of high doses of loop diuretics may result in hypovolaemic hyponatraemia by inducing overt volume depletion. Loop diuretics because of their effect on urine concentrating ability typically do not cause severe hyponatraemia. By preventing active sodium reabsorption in the loop of Henle, loop diuretics make the medullary interstitium hypotonic and typically lead to excretion of urine with a concentration of about 0.45% saline (75 mEq/1).

Diuretic induced K^+ depletion can also lead to hyponatraemia, independent of the effects of Na^+ depletion. Hypokalaemia impairs the urinary concentrating ability and can lead to nocturia, polyuria and polydipsia.

In most cases, diuretic induced hyponatraemia will resolve by

discontinuing the diuretic. Once the patient becomes euvolaemic, ADH release will be appropriately suppressed and rapid excretion of the excess water occurs. If patient is symptomatic, hypertonic saline can be slowly infused for gradual sodium correction.

Another important cause of hypotonic-hypovolaemic hyponatraemia is CSW. It is a rare syndrome described primarily in patients with intracranial disease such as infections, cerebrovascular accidents, tumours and neurosurgery that may lead to renal salt wasting and volume contraction in some patients. The mechanisms implicated in impaired renal tubular sodium reabsorption include decreased sympathetic tone that normally promotes sodium, uric acid and water reabsorption in the proximal tubule, increased production of brain natriuretic peptide (BNP) that inhibits renin release and decreases sodium reabsorption in proximal and distal tubules. The typical onset of hyponatraemia because of CSW is within 10 days following the neurological insult and is rarely seen after 30 days.

As SIADH is the most common cause of hyponatraemia in patients with intracranial disease, it should be carefully differentiated from CSW. Treatment of CSW should be attempted with isotonic saline. Volume repletion will suppress the release of ADH resulting in the excretion of the excess water and correction of the hyponatraemia. Salt tablets and fludrocortisone can be also be used to treat CSW. As CSW is usually transient, long-term therapy is not necessary.

Table 3: Comparative profile of the syndrome of inappropriate ADH secretion (SIADH) and cerebral salt wasting (CSW)

Clinical features	**SIADH**	**CSW**
Plasma sodium	Low	Low
ECF volume	Normal or slightly	Decreased
Total body water volume	Increased	Increased
Blood pressure	Normal	May be low
Postural hypotension	Absent	Present
Antidiuretic hormone	Increased	Increased
Urine osmolality	Inappropriately high	Appropriately high
Urineosmolalityaftervolumeexpansion	Relatively fixed	Decrease to <100mOsm/kg
Urinarysodium excretion	Increased >40 mEq/1 because of volume expansion	Increased >40 mEq/1 because of salt wasting
Plasma uric acid level	Low due to volume expansion	Low due to urinary losses
Fractional excretion of urate	Normal after correction of plasma sodium	Elevated after correction of plasma sodium
Brain natriuretic peptide	Normal	Normal to high
Effect of isotonic saline	May worsen	Improves hyponatraemia
Treatment	Free water restriction, hypertonic saline infusion, ADH antagonists, loop diuretics, high solute intake, Demeclocycline	Salt loading volume replacement, fludrocortisone acetate

Hypervolaemic-hypotonic hyponatraemia

Hypervolaemic-hypotonic hyponatraemia results from water retention in excess of sodium retention in the face of elevated total body sodium content. The most common causes are cardiac disease, cirrhosis, renal failure and nephrotic syndrome. With the exception of renal failure, these states are characterised by avid Na^+retention (urinary Na^+concentration <10 mEq/1) that may be obscured by the concomitant use of diuretics.

The decreased ECV in CHF despite increased ECF volume leads to activation of the RAA and sympathetic nervous systems along with ADH release to promote sodium and water retention. The retained solute and volume extravasate from the intravascular space to ECF causing dilutional hyponatraemia. Persistent hyponatraemia is associated with an adverse short-term and long-term prognosis in patients with acute myocardial infarction and heart failure. Restricting water intake combined with angiotensin converting enzyme (ACE) inhibitors and loop diuretic is the mainstay of therapy in hyponatraemic patients with cardiac dysfunction. Vasopressin receptor antagonists such as conivaptan and tolvaptan produce a selective water diuresis without affecting sodium excretion and may have a role in the management of hyponatraemia associated with heart failure.

In cirrhosis, ECV is decreased because of splanchnic vasodilatation

induced possibly by nitric oxide.This leads to activation of RAA system and ADH release, and the latter is roughly proportional to the severity of the cirrhosis. Hyponatraemia (<130 mEq/1) is a powerful predictor of prognosis and death, in patients with cirrhosis waiting for the liver transplantation. As symptomatic hyponatraemia is unusual in cirrhosis, the mainstay of therapy is restricting water and salt intake combined with diuretics. Vasopressin receptor antagonists may also have a role in the management ofhyponatraemia associated with cirrhosis.

Nephrotic syndrome typically results in sodium retention induced by the renal disease and decreased ECV caused by the low plasma oncotic pressure. The incidence of hyponatraemia in the nephrotic syndrome is lower compared with both CHF and cirrhosis.

Sodium and water balance are usually maintained in patients with chronic renal failure, until the GFR falls below 10-15 ml/min. Patients with advanced renal failure have impaired free water clearance, and the minimum urine osmolality is 200-250 mOsm/kg despite the appropriate suppression of ADH. Hypervolaemic hyponatraemia occurs when the water intake exceeds the ability to excrete equivalent volumes. When hyponatraemia develops in patients with renal failure, the plasma osmolality may be normal or high because of the retention of urea (ineffective osmole), but their corrected or effective plasma osmolality will remain normal and is calculated as follows.

Corrected plasma osmolality = Plasma osmolality - (BUN + 2.8)

Hyponatraemia of chronic renal failure generally responds to the combination of dietary sodium and water restriction combined with diuretic therapy

Euvolaemic hypotonic hyponatraemia

The broad differential diagnosis of Euvolaemic hypotonic hyponatraemia includes the syndrome of inappropriate ADH (SIADH),adrenal insufficiency, hypothyroidism, medications, exercise-induced . ADH directly or indirectly mediates these processes. Beer potomania , primary polydipsia and reset osmostat are exceptions to the latter , urinary sodium excretion is typically normal in all of the above conditions ,Only excess ADH release conditions are associated with an elevated urine osmolality.

Decreased GFR and renal plasma flow has been shown to be associated with Hypothyroidism.Levels of ADH are elevated with severe hypothyroidism, and thyroxine replacement corrects the elevated ADH levels.The impaired water excretion in this disorder is being mediated by the excess ADH combined with diminished distal fluid delivery

Glucocorticoids play a pivotal role in the normal water excretion, elevated ADH levels are seen in glucocorticoid defeciency.Physiological doses of glucocorticoids corrects these elevated ADH levels.Renal hemodynamics gets altered in prolonged glucocorticoid deficiency (14-17 days) ,because water excretion is impaired by an ADH independent process.

Continued ADH secretion and excessive hypotonic fluid intake contributes to the exercise-associated hyponatraemia (EAH) seen after endurance exercise (e.g. triathlon events and marathons) . Hypovolaemia because of sweat losses, intense exercise pain and emotion constitutes the Non-osmotic stimuli for the ADH secretion in endurance athletes . Dizziness, nausea and vomiting to seizures, coma and death are the various clinical signs and symptoms due to acute hyponatremia seen in exercise associated hyponatremia

Fluid restriction and observation until the onset of a spontaneous diuresis should be the management protocol for hyponatraemic patients with mild to moderate symptoms . Where as hypertonic saline should be given for those with severe neurological symptoms till the resolution of neurological symptoms. Prevention of these conditions can be done by training the endurance athletes to drink according to thirst during the race.

Primary polydipsia also comes under euvolemic hyponatremia.Water consumption in excess of 10 to 151 a day has been seen in many patients with chronic psychiatric illnesses notably schizophrenia .Suppression of ADH secretion occurs as a result of this excess water consumption and patient begins to excrete dilute urine (osmolality nearly 50mosm/kg) .Maintainence of euvolemia also happens as a result of sodium excretion via renal route (urine sodium >20 mEq/1). A defect in regulation of thirst centrally possibly plays a pivotal role in

the pathogenesis of polydipsia.[43]Acutely psychotic patients are at an increased risk for developing hyponatraemia and treatement with some antipsychotic medications also add on the risk by increasing thirst through anticholinergic side effects. Augmented vasopressin release can be seen in schizophrenic patients with hyponatraemia during psychotic exacerbations. Long-term management options include limiting the fluid intake, restricting the use of drugs causing dry mouth etc.

The hyponatraemia in beer potomania arises in patients who are consuming large amounts of beer along with intake of very low solute . In malnourished patients who are consuming low-protein, high-water diets,a similar form of hyponatremia is being described;where the endogenous protein breakdown and urea excretion are suppressed by the high carbohydrate load .

Plasma osmolality and plasma sodium are maintained at a lower set point in patients with reset osmostat.They can dilute or concentrate the urine in response to water loading and dehydration since the functioning of osmoreceptor is normal eventhough its set around a new baseline . Patients typically presentation occurs within a stable range of mild to moderate hyponatraemia (between 125 and 135 mEq/1). The diagnosis can be confirmed clinically by giving excess water and observing the response to this water load, where patients with reset osmostat typically excrete >80% of ingested water within few hours.

Downward resetting of the osmostat is a normal consequence of

pregnancy, which results in a decreased plasma osmolality of approximately 10 mmol/kg and an increase in plasma volume. The shift in osmotic threshold appears in the first trimester and persists throughout pregnancy, returning to normal by 2 weeks after delivery. Reset osmostat has been also described in patients with quadriplegia, psychosis, tuberculosis, chronic malnutrition, cachexia, hypothalamic tumours and hypothalamic injury from trauma or surgery. As attempting to raise the serum sodium concentration is likely to be ineffective, treatment should be primarily directed at the underlying disease.

Hyponatraemia is also found in up to 50% of hospitalised and 20% of ambulatory patients with human immunodeficiency virus (HIV) infection. The aetiology is multifactorial and includes SIADH secondary to drugs, encephalopathy or secondary infections such as cytomegalo virus, hepatitis C or toxoplasmosis, depletion because of chronic diarrhoea, renal tubular toxicity associated with therapy and adrenal insufficiency.

Hyponatraemia of unknown aetiology should prompt a work up for neuroendocrine amine precursor uptake and decarboxylating (APUD) tumours as well as oat cell, breast and ovarian tumours that are often difficult to detect.

One of the aetiologies of euvolaemic hypotonic hyponatraemia that is commonly diagnosed in hospitalised patients is the SIADH.

Syndrome of inappropriate ADH secretion (SIADH)

The SIADH is associated with increased morbidity and mortality of hospitalised patients and is a measure of the severity of the underlying illness. Under normal circumstances, hypovolaemia and hyperosmolality 'appropriately' stimulate ADH secretion. ADH release is considered 'inappropriate' without these physiological cues. High levels of vasopressin are secreted intermittently at an abnormally low threshold or continuously despite low osmolality. The presence of hyponatraemia with a urine osmolality higher than maximal dilution confirms the diagnosis. Nausea and pain are potent stimulators of ADH release and commonly lead to SIADH in hospitalised postoperative patients.

Table 4: Drug-induced hyponatraemia causes

Anti-psychotics	**Anti-depressants**	**Anti-convulsants**	**Analgesics and Recreational Drugs**
Phenothiazines Haloperidol	SSRI's TCA's	Carbamazepine Oxcarbazepine	Morphine (high doses), Tramadol, MDMA (Ecstasy), NSAID's, Colchicine, Venlafaxine, Cymbalta (duloxetine)
Cardiac drugs	**Anti-diabetics**	**Anti-neoplastic agents**	**Antibiotics**

Thiazides, clonidine, ACE inhibitors, Aldosterone antagonists, Amiloride, Loop diuretics, Methyldopa, Amlodipine, Amiodarone, lorcainide, Propafenone, Theophylline, Terlipressin, Unfractionated heparin (aldosterone antagonist)	Chlorpropamide, Tolbutamide, Glipizine	Cyclophosphamide, Vincristine, Vinblastine Cisplatin, Hydroxyurea, Melphalan	Azithromycin Trimethoprim-sulfamethoxazole, ciprofloxacin, cefoperazone/ sulbactam, rifabutin
	Lipid lowering agents	**Immunosuppressive drugs**	**Gastrointestinal drugs**
	Clofibrate	Tacrolimus, Methotrexate, interferon a and y, levamisole, Monoclonal Antibodies	Somatostatin analogs, Omeprazole
			Others
			Bromicriptine

Table 5: Non-drug induced causes of the syndrome of inappropriate ADH

Non-osmotic stimuli	CNS lesions	Malignancies	Increased intrathoracic pressure
Nausea	Tumours (neuroblastoma)	Lymphoma, leukaemia, and Hodgkin disease	Mediastinal tumours (thymoma, sarcoma)
Pain	CVA	Carcinoma of the uterus	Positive pressure ventilation
Stress	Meningitis	Ureteral, prostate, bladder carcinoma	Infections (pneumonia, TB, aspergilosis, long abscess)
HIV	Encephalitis	Carcinoma of duodenum and pancreas	Bronchogenic carcinoma, mesothelioma
Acute psychosis	Abscess	Ectopic production of vasopressin by tumours (small cell lung carcinoma, carcinoids)	Bronchogenic carcinoma, mesothelioma
Acute psychosis	Abscess	Ectopic production of vasopressin by	Bronchiectasis

		tumours (small cell lung carcinoma, carcinoids)	
Surgery	Guillain-Barre syndrome	Cancers of the head and neck and nasopharynx	Empyema
Pregnancy (physiological)	Hydrocephalus	Renal cell carcinoma	Chronic obstructive pulmonary disease
Hypokalaemia	Pituitary stalk lesion	Osteosarcoma	Pneumothorax
CHF exacerbation	Delirium tremens Demyelinating disease Acute porphyria	Osteosarcoma	Pneumothorax

In many patients, the initiating event of SIADH is ingestion of water that is not excreted because of the elevated vasopressin. Although water is retained in hyponatraemia, approximately 60% of the excess fluid goes into the cells. This leads to the expansion of extracellular and intracellular volume with an associated natriuresis of isotonic urine in an effort to bring the ECF volume back to normal.

Sometimes it is difficult to differentiate SIADH from mild to moderate

depletional hyponatraemia caused by renal losses (e.g. diuretic use). The response of urinary and plasma sodium concentration to an infusion of 1-2 1 of 0.9% saline may help in the differential diagnosis. In the patient with SIADH who is at equilibrium, the administered saline will be excreted and therefore there will be an increase in urinary sodium, while plasma sodium concentration will either not change or decrease slightly. If the patient has depletional hyponatraemia from renal losses, sodium from the administered saline will be retained and the excess water is excreted. There will be a decrease in urinary sodium, while the plasma sodium concentration will rise.

Laboratory and clinical features of SIADH include the following:

(1)Euvolaemic hyponatraemia;

(2)Decreased measured plasma osmolality (<275 mOsm/kg);

(3)Urine osmolality > 100 mOsm/kg;

(4)Urine sodium usually > 40 mEq/1;

(5)Normal acid-base and potassium balance;

(6)BUN < 10 mg/dl (3.57 mmol/1);

(7)Hypouricemia <4 mg/dl (238umol/l);

(8)Normal thyroid and adrenal function and

(9)Absence of advanced cardiac, renal, or liver disease.

There is an over-reliance in clinical practice on plasma: urine osmolality ratios that can be misleading and absolute values of plasma and urine osmolality

are far better indicators of the diagnosis. In clinical practice, ADH levels are not required to be measured in patients with suspected SIADH. However, in some clinical centres where ADH assays are readily available, the measurements may be helpful.

It is a common misconception to expect urine osmolality to be higher than that of serum osmolality in patients with SIADH. The latter is more often seen in patients with depletional hyponatraemia. In euvolaemic patients with SIADH, urine osmolality above 100 mOsm/kg is inappropriately high and is an indirect measure of persistent ADH secretion. Patients with SIADH may have a low urine sodium concentration if they are also volume depleted or if their sodium intake is extremely low. In such patients, the diagnosis of SIADH is confirmed by 0.9% saline loading as describe above (i.e. the urine sodium rises, but the urine osmolality remains high).

The low BUN and plasma uric acid concentrations in patients with SIADH are partly dilutional, but also result from increased urea and uric acid clearances in response to the ECF volume expansion.

Clinical features of hyponatraemia

Although most hyponatremic patients may appear asymptomatic, severe symptomatic hyponatremia is a medical emergency that calls for immediate treatment. Signs and symptoms depend on several factors and vary by patient. The rate of decline in serum sodium concentration, the patient's age, and the

volume of extra cellular fluid (ECF) all affect the clinical presentation.

CNS symptoms

Symptoms are related largely to dysfunction of the central nervous system and are more evident when the decrease in the serum sodium concentration is large orfast. However, patients also present with non-neurologic symptoms, such as fatigue, thirst, weakness, cramping, nausea, vomiting, bloating, swelling, and tightness of the hands and feet. Most patients with a serum sodium concentration greater than 125 mEq/L or with chronic hyponatremia do not have neurologic symptoms, owing to volume adaptation by the brain.

Gastrointestinal symptoms, such as nausea and vomiting, are more common in patients with serum sodium levels between 125 and 130 mEq/L.Acute hyponatremia (<48 hours in duration) in a previously asymptomatic young adult can cause severe central nervous system symptoms even at serum sodium levels between 125 and 130 mEq/L. Once the level falls below 125 mEq/L, neurologic symptoms predominate. Headache, muscle cramps, reversible ataxia, psychosis, lethargy, restlessness, disorientation, apathy, anorexia, and agitation are symptoms seen in patients with serum sodium levels below 125 mEq/L.

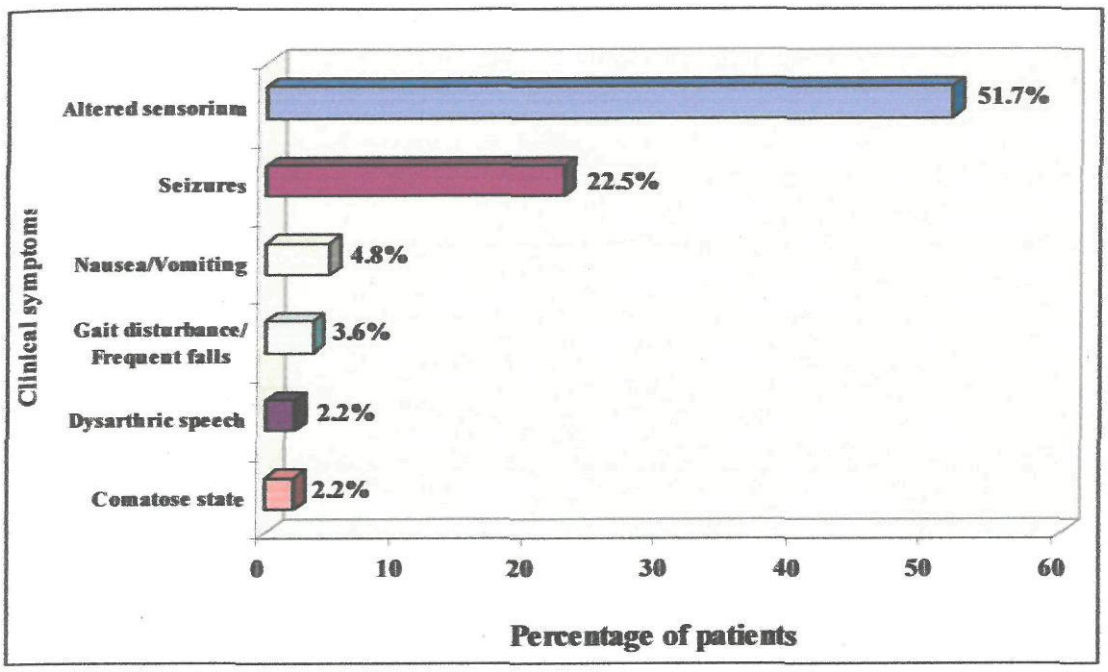
Clinical signs include abnormal sensorium hypothermia, depressed reflexes, pseudobulbar palsy, and Cheyne-Stokes respiration.

Complications of severe hyponatremia

Complications of severe and rapidly developing hyponatremia includeseizures, coma, brainstem herniation, respiratory arrest, permanent brain damage, and death. These complications result primarily from hyponatremia induced cerebral edema, which is most often seen in patients following surgery or in those with primary polydipsia. Menstruating women are also at elevated risk of severe neurologic complications associated with hyponatremia.

Clinically important hyponatremia is a particular challenge in patients with acute neurologic diseases such as cerebral salt-wasting syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), anoxic or traumatic brain injury, or subarachnoid hemorrhage, since the presentations can overlap significantly.

Figure 2: Clinical symptoms in severe nyponatremia



Distinction between acute and chronic hyponatraemia is clinically important because chronic hyponatraemia is surprisingly well-tolerated, even at very low levels of serum sodium, and overly aggressive treatment may result in serious neurological sequelae. Aggressive initial correction is warranted in patients with acute symptomatic hyponatraemia, which can potentially cause irreversible neurological damage and death.

Hyponatraemia is considered acute when it develops within 48 h of prior normal plasma sodium levels. Acute hyponatraemia occurs most often with intake of large volumes of hypotonic fluids (postoperative patients, marathon runners) and also in users of 'ecstasy' (3,4-memylenedioxymethamphetamine, MDMA). As a result of osmotic effect, water moves intracellularly and results in cerebral oedema. Eventually, the extracellular water is moved into the cerebrospinal fluid, and cerebral oedema gradually resolves by extruding sodium and potassium salts and certain organic solutes called osmolytes.

Hyponatraemia is considered chronic if it develops slowly and persists for greater than 48 h.[53] Patients with chronic gradual onset hyponatraemia are typically asymptomatic because of the brain adaptation to changes in osmolality. This adaptation occurs at the expense of loss of intracellular osmolytes, which normally protect the brain from a sudden increase in osmolality of the ECF. In these patients, rapid increase in plasma osmolality results in water moving out of neurons, leading to shrinkage of cerebral tissue.This is the possible mechanism of

central myelinolysis, which was first described in the pons, but can occur diffusely throughout the brain.

Neurological deterioration typically develops over several days with fluctuating consciousness, convulsions, hypoventilation and hypotension. Eventually, patients may develop pseudobulbar palsy with difficulty in swallowing, inability to speak and quadriparesis. Recovery from this syndrome is variable, and many neurological complications are permanent. The magnetic resonance imaging (MRI) scans demonstrate the demyelinated lesions 3-4 weeks after the correction of hyponatraemia.

Hyponatraemic encephalopathy is more likely to develop in patients who suffer a hypoxic event and have underlying severe liver disease, and in premenopausal women.As there is no effective therapy after the development of central demyelination, prevention is of primary importance.

MANAGEMENT OF HYPONATREMIA

To be optimal, therapy for hyponatremia must be individualized. In all patients, the risk of hyponatremia-associated complications must be balanced against the risk of serum sodium correction. Several important factors should be considered when deciding on treatment, including the following:

- The rapidity of onset of hyponatremia
- The degree, duration, and symptomatology of hyponatremia
- The presence or absence of risk factors for neurologic complications.

Acute symptomatic hyponatremia

Acute symptomatic hyponatremia develops in less than 48 hours. Clinical manifestations are largely related to central nervous system dysfunction resulting from brain cell swelling. Patients are at particular risk for this condition during the perioperative period. Once the serum sodium level falls below 125 mEq/L, neurologic symptoms predominate. In acute severe and rapidly developing hyponatremia, the risk of complications of cerebral edema exceeds the risk of osmotic demyelination associated with too-rapid correction of serum sodium, so treatment should begin promptly.

Prompt, controlled correction of the serum sodium level is indicated for patients with acute symptomatic hyponatremia. The goal is to raise the serum sodium level by 1.5 to 2 mEq/L/hour until symptoms subside 1 or until the concentration has risen to a safer level—usually greater than 118 to 120 mEq/L, with the primary focus being to minimize the risk of seizures. Even in symptomatic patients, the sodium level should not be raised by more than 12 mEq/L in the first 24 hours and by more than 18 mEq/L in the first 48 hours, in order to avoid osmotic demyelination (central pontinemyelinolysis).

Infusion of hypertonic saline (3%) at a rate of 1 to 2 mL/kg/hour and addition of a loop diuretic, to enhance water excretion, are commonly used to achieve this goal.Hypertonic saline may be infused at a rate of 4 to 6mL/kg/hour if severe neurologic symptoms, particularly seizures, are present. Once a patient

is asymptomatic and sodium levels are greater than 118 mEq/L, correction should be slowed to no more than 8 mEq/L in 24 hours to achieve a target level of 125 mEq/L. In all cases, close and frequent monitoring of serum sodium and electrolytes is mandatory until sodium levels increase and symptoms subside.

Chronic symptomatic hyponatremia

In hyponatremia of unknown duration, or of more than 48 hours' duration, sodium correction should be managed very cautiously because of significant osmotic adaptation of the brain to prolonged hyponatremia. In patients presenting with severe symptoms, treatment should be similar to that for acute symptomatic hyponatremia: hypertonic saline plus a loop diuretic. Careful monitoring is critical because of an increased risk of irreversible osmotic demyelination. Correction should be limited to no more than 10 to 12 mEq/L on the first day of treatment and less than 6 mEq/L/day thereafter. In patients presenting with mild to moderate symptoms, slower correction is required, generally 0.5mEq/L/hour. Once the desired correction is achieved, therapy may continue in the form of fluid restriction.

Chronic asymptomatic hyponatremia

The goal in treating asymptomatic hyponatremia is to prevent a further decline in serum sodium and to maintain levels as close to normal as possible. Treatment involves a more conservative approach than for symptomatic hyponatremia. Initially, underlying causes of hyponatremia should be

investigated and treated; this should include evaluation for drug-induced hyponatremia. Fluid restriction, isotonic saline, and loop diuretics maybe used to treat the hyponatremia.

Euvolemic hyponatremia is the most common form of asymptomatic hyponatremia. If the underlying cause is SIADH and its etiology is unknown or cannot be effectively treated, therapy should be instituted for the hyponatremia itself. '[5]In cases where the etiology of SIADH is known (e.g. tumor), the underlying cause should be treated or removed in addition to correcting the serum sodium level.

Management of the SIADH should begin with water restriction and treatment of the underlying aetiology, such as stopping inciting medications, treatment of nausea, pain, infections and chemotherapy for cancer. In all patients with hyponatraemia, free water intake from all sources should be restricted to less than 1-1.5 1/day. The negative water balance caused by water restriction will gradually increase the serum sodium concentration. In patients with mild symptoms, the rate of urinary solute excretion, the main determinant of the urine output, can be increased by a high salt, high protein diet or supplementation with urea (30-60 g/dl) or salt tablets (200 mEq/day). However, salt therapy is generally contraindicated in patients with hypertension and oedema, as it leads to exacerbation of both conditions.

Symptomatic or severe hyponatraemia generally requires hospitalisation

for observation, careful monitoring of fluid balance and body weight and frequent measurements of plasma sodium concentrations. Giving hypotonic fluids in the setting of elevated ADH levels can produce severe and life-threatening hyponatraemia. Electrolyte concentrations and osmolalities of commonly used intravenous fluids are listed below:

Table 6: Electrolyte concentration and osmolality of commonly used intravenous fluids

11 infusate*	Na^+ (mEq/1)	C1 (mEq/I)	H_20 (ml)	Change in ICF (ml)	Change in ECF (ml)		Osmolality (mOsm/kg)
					Total	Intra-vascular	
0.9% saline 11	154	154	0	0^+	1000^+	250 ml^+	308
3% saline 11**	513	513	0	Decreased due to osmotic shift	1000+ water drawn from ICF	Increased	1026
5% saline 11**	855	855	0	Decreased due to osmotic shift	1000+ water drawn from ICF	Increased	1710
Ringer's lactate 11	130	109	0	100	900	225	273
0.45% saline 11	77	77	500	335	665	166	154
D5W	0	0	1000	667	333	83	253

ICF=Intracellular fluid; ECF=Extracellular fluid; TBW=Total body water.

* Assumes: ICF=2/3rd TBW; ECF=l/3rd TBW; Intravascular (plasma)

volume=l/4,[h] ECF.

+ Only in patients with normal plasma osmolality. Hypertonic for a patient with hyponatraemia. ** Changes in ECF and ICF volume are dependent on patient's degree of hyponatraemia.

One can directly calculate the degree to which saline infusate would initially raise the plasma sodium concentration. The increase in plasma Na concentration (P(Na)) can be calculated with the following equation:

Estimated increase in $P[Na^+]$ = (Infusate $[Na^+]$ - $P[Na^+]$) + (TBW)

As such computed estimates are not capable to precisely predict the magnitude of change, the sodium concentration should be monitored as frequently as every 1-2 h. It isalso noteworthy that normal (0.9%) saline is usually sufficient for the management of most cases of hyponatraemia, and the risk of cerebral symptoms with hypertonic saline is significant unless close monitoring is performed.

A recent alternative to saline administration in the management of hyponatraemia is the use of ADH receptor antagonists. The most specific treatment for SIADH is to block the V2 receptors in the kidney that mediate the diuretic effect of ADH. Vasopressin antagonists are currently indicated for the treatment of euvolaemic and hypervolaemic hyponatraemia, and these agents are usually preferred if SIADH or ADH is the cause. For hospitalised patients, conivaptan is given as an intravenous loading dose of 20 mg delivered over 30

min, then as 20 mg continuously over 24 h. Subsequent infusions may be administered every 1-3 days at 20-40 mg/day by continuous infusion. Rapid correction of hyponatraemia has been reported in patients receiving conivaptan. Therefore, frequent checks of plasma sodium are needed. Each vial (20 mg/4 ml) of conivaptan typically costs approximately $500 and when used over 3 days at the recommended doses, the total cost of such infusion could reach $3000.

More recently, an orally active vasopressin receptor antagonist tolvaptan became available. The efficacy of oral tolvaptan in ambulatory patients with SIADH, heart failure and cirrhosis has been recently demonstrated. V2-receptor antagonists are not suitable for certain causes of hyponatraemia, such as CSW syndrome, psychogenic polydipsia and potomania.

While SIADH is frequently a transient phenomenon, a chronic phase can occur in patients with ectopic ADH producing tumours and in patients where antipsychotic drugs cannot be discontinued. If water restriction and salt tablet therapy are ineffective in these patients, the following drug therapy to antagonise the effect of ADH could be attempted: (i) administration of loop diuretic along with salt tablets; (ii) demeclocycline; (iii) lithium carbonate; and (iv) orally active vasopressin antagonists such as tolvaptan.

Administration of loop diuretic (20 mg furosemide orally twice a day) along with salt tablets will not only antagonise the effect of ADH but also prevents the oedema formation by the latter.

Demeclocycline (300-600 mg orally twice a day) inhibits the effect of ADH in the collecting tubule.Its onset of action may require 1 week, and urinary concentrating ability may be permanently impaired, resulting in nephrogenic diabetes insipidus and even hypernatraemia. Demeclocycline is nephrotoxic in patients with cirrhosis and is contraindicated in children because of interference with bone development and teeth discoloration.

Lithium carbonate (300 mg orally twice a day) also inhibits the effect of ADH. It is less effective than demeclocycline and when used chronically, it may induce interstitial nephritis and renal failure. Therefore, lithium should be considered for use only in patients in whom demeclocycline is contraindicated, such as children and patients with liver disease.

Table 7: Treatment options for hyponatremia

Treatment	**Mechanism**	**Limitations**
Fluidrestriction (most common)	Induces negative water balance Increases plasma osmolality and serum sodium	No direct inhibition of excess hormone No inhibition of hormone on kidneys Nonadherence
Demeclocycline	Impairs AVP action at renal tubules Induces nephrogenic diabetes insipidus	Nephrotoxicity (cirrhosis patients) Hypersensitivity Drug interactions Unsafe in pregnancy

	Reduces urine concentration, even with increased AVP levels	
Urea	Decreases sodium excretion	Hypersensitivity Unsafe in pregnancy Azotemia Liver failure Can reduce effects of lithium Phlebitis, thrombosis
Lithium	Impairs AVP at renal tubules	Inconsistent results Lithium toxicity Anti-anabolic effects mainly in cirrhosis and congestive heart failure Unsafe in pregnancy
Diuretics (loop/thiazide)	Increase water excretion by inhibiting sodium and chloride reabsorption in loop of Henle and distal tubule	Hypersensitivity Hepatic coma Anuria Severe electrolyte depletion

COMPLICATION OF TREATMENT

Central Pontine Myelinolysis (CPM) has traditionally been associated with rapid correction of hyponatremia, but the etiology has not been clearly established.

PATHOGENESIS

The pathogenesis of CPM is unknown, but the theories such as the osmotic hypothesis of CPM have implicated hyponatremia and its rapid correction in some cases.It is postulated that cells conditioned to a hypoosmotic hyponatremia environment may have a decreased adaptive capacity to osmotic stress.

The predilection of the myelinolysis to the pons is thought to be a result of the grid arrangement of the oligodendrocytes in the base of the pons, which limits their mechanical flexibility and therefore their capacity to swell. During hyponatremia these cells can only adapt by losing more ions instead of swelling, making them prone to damage when sodium is replaced. Proximity to the extensively vascularised gray matter makes the pons particularly susceptible to damage caused by vasogenicodema and myelinotoxic substances from vessels.

CLINICAL PRESENTATION

The clinical presentation is highly variable, can present with a rapidly evolving paraparesis or quadriparesisand pseudobulbar palsy. They may present with locked in syndrome, in which intellectual activity is preserved but cannot be expressed. Less often it can manifests with ataxia, other movement disorders or behavioural symptoms.

DIAGNOSIS

Diagnosis of CPM is based on clinical suspicion and is confirmed by imaging studies. MRI is the primary method for diagnosis and is superior to CT.

during the acute phase, symmetrical and hypointense lesions on a TI weighted MRI can be identified.In comparison, during the subacute phase there are symmetrical and

hypointense lesions in T2 weighted images.

MANAGEMENT

The most important step in the management of CPM is recognising the patient at risk and preventing rapid correction of hyponatremia-especially chronic severe hyponatremia. Once a diagnosis is made, the management of CPM is mainly supportive.

Treatment modalities

- Thyrotropin releasing hormone
- Methylprednisolone
- Plasmapheresis
- Immunoglobulins.

The exact mechanism of action of TRH, corticosteroids, and plasmapheresis is unknown. A conservative approach with treatment of the precipitating or underlying conditions and appropriate supportive care in severe cases may be justified in the absence of studies confirming the efficacy of the above mentioned treatments.

REVIEW OF LITERATURE

In a hospital based descriptive study of symptomatic hyponatremia in elderly patients conducted by Rao et al. including 100 patients with symptomatic hyponatremia, they concluded hyponatremia is commoner among females and females will tolerate hyponatremia better than their male counterparts. Lethargy (feeling of tiredness), irrelevant talk and drowsiness with delayed latent period and slow response were concluded as most common problems noticed by the patient. Around 61% of patients were assigned to be euvolemic, 23% were found to be overloaded and 16% found to be dehydrated. Isovolemic hyponatremia was concluded to be the most common type. The common causes of hyponatremia were SIADH(30%) followed by drugs(25%).

Mahavir, Agarwal et al compared the clinical and aetiological profile of low serum sodium presenting to the emergency department with that developing during the in- hospital stay .common symptoms were concluded as confusion (41%), headache (40%) and malaise (38.6%). Most common cause was found to be poor intake(82.9%),and increased losses was found to be the next common cause. 31.4% developed low serum sodium during their in-hospital stay. Most common precipitating events for the hyponatremia in hospitalised patients were found to be due to improper ryle's tube feeding,volume overload and drugs.

In a study done on the etiology and the frequency of hyponatremia in adult

hospitalized patients in medical wards of a general hospital by Thomas Vurgese et al. 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 122 mmol/litre. 59.1% patients presented during earlier summer months as compared to 40.9% who presented during winter months. Commonest cause of hyponatremia was concluded as SIADH due to pneumonia.

Miyashita J et al., in a study on impact of low serum sodium and SIADH on mortality in aged patients with pneumonia due to aspiration, concluded that low serum sodium levels due to SIADH had a strong correlation with increased death rate in elderly patients. out of 221 cases 29% were suffering from low serum sodium levels. Of these 95% had hypotonic hyponatremia, which were further assessed as having hypovolemic (63%), hypervolemic (5%) and euvolemic (32%) hyponatremia. Of the euvolemic patients 70% had SIADH. There were significant increase in mortality with both severe and moderate decrease in serum sodium levels.30 day mortality was significantly higher in adult patients with SIADH

Rubio Rivas H et al. conducted a study on geriatric patients with low serum sodium levels and assessed its prevalence and prognosis. The sample consisted of 52.7% females and 47.2% males. Mean age was 83.7 years. Mean plasma sodium values were 137.3 mmol/litre. Emergency lab test showed, out of 60 patients with

hyponatremia 35 were in Acute geriatric care unit. Most common predisposing factors were cardiopulmonary illnesses. Mean hospital length of stay was 12.8 days. In-hospital mortality was 12.9%).

They observed a statistically significant association between mean serum sodium levels and duration of hospital stay. No significant association was found between serum sodium levels and death rate.

Chua M et al. studied on prognostic implications of hyponatremia in elderly patients and concluded that low serum sodium levels during initial presentation were strongly associated with increased mean length of in hospital stay and advanced dependence. This cohort study measured the prognostic impact of hyponatremia in all patients admitted to 2 acute geriatric wards. Basic demographic data and serum sodium results were included in multiple linear and logistic regression models for the end points, length of stay and return to previous residence respectively. There were 103 cases (mean age 82, 59% females),of whom 18% were hyponatremic on admission, but another 23% became hyponatremic whilst in hospital. Median length of stay was 13 days. 65% cases returned to the previous residence on discharge, 8% died. Factors independently associated with longer length of stay were increasing age, lower admission serum sodium and larger drop in serum sodium during admission. Only a larger drop in serum sodium was significantly associated with failure to return to previous residence.

MATERIALS AND METHODS

SOURCE OF DATA

The study was conducted in Madurai medical college during the period from april to September 2016. Patients aged ≥ 60 years admitted with serum sodium < 135 meq/1 were included in the study.

INCLUSION CRITERIA

Subjects aged ≥ 60 years with serum sodium < 135 meq/1 (Government of India defines 'senior citizen' or 'elderly' as a person who is of age60 years or above)

Patients with euvolemic hyponatremia(SIADH,hypothyroidism etc

EXCLUSION CRITERIA

Patients aged < 60 years

Serum sodium ≥135 meq/1

Patients with hypovolemic and hypervolemic hyponatremia(CCF,CKD,CLD)

MATERIALS AND METHODS

Clinical assessment

Detailed history: (based on inclusion and exclusion criteria).This included history of symptoms of hyponatremia, predisposing factors and pre-existing illness if present. The definition of symptomatic hyponatremia was based on a clinical assessment of symptomatology including the presence of altered sensorium, postural dizziness, lethargy and seizures. Sensorium changes

included acute confusional states, memory disturbances, stupor, delirium and coma. Drugs that can cause hyponatremia were recorded. History of illness causing hyponatremia such as CCF, CKD, CLD,(exclusion criteria) hypothyroidism and other conditions which are associated with SIADH such as small cell carcinoma, CNS disease were taken. History of fluid loss as in vomiting, diarrhoea, diuretic use, exceesive sweating were taken in all patients

Physical examination: Detailed clinical examination was done in every patient. Hydration status of the patient was determined by clinical examination. The signs of hypovolemia included tachycardia, decreased skin turgor, dry mucous membranes and decreased peripheral perfusion. Hypervolemic state was defined by the presence of anasarca,ascites, bilateral pitting pedal oedema and raised JVP. Accordingly patients were divided into hypervolemic, hypovolemic and euvolemic.

SIADH and CSW were differentiated on the basis of volume status of the patient,urine osmalility after volume expansion,treatement and response to treatement.

At the time of diagnosis of hyponatremia, detailed CNS examination was done to document mental status of the patient and other focal neurological deficit. CNS examination was repeated after the correction of hyponatremia and the presence of symptoms such as dizziness, lethargy, altered sensorium and seizures were attributed to hyponatremia unless there was a co-existing medical condition or medication effect to account for these symptoms. Patients were screened for CPM based on clinical grounds that is development of confusion, agitation and

flaccid or spastic paralysis during or after correction of hyponatremia.

Investigations

1. CBC: Hb, TLC, DC, Plt count
2. URE, microscopic examination and specific gravity
3. Serum sodium: Serum sodium was done daily for symptomatic cases, alternate days for asymptomatic patients.
4. Serum BUN and glucose levels: For calculation of serum osmolality.
5. Serum osmolality was calculated by the formula

   Serum osmolality = 2(sodium) + RBS/18+BUN/2.8

Patients were divided into

- Isotonic - 280-295 mosm/1
- Hypotonic - <280 mosm/1
- Hypertonic - >295 mosm/1

6. Urine osmolality- in patients with hypotonic hyponatremia.
   (normal range-300-900 mosm/kg)
7. Urine sodium- in hypotonic hyponatremic patient.
   (normal range-40-220 meq/1)
8. Brain imaging and CSF analysis in patients presenting with altered sensorium to exclude structural abnormalities and meningeal infection.
9. Serum protein and lipid profile to rule out pseudohyponatremia
10. Thyroid function test and serum cortisol

Management and Outcome Assessment

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

Category	Serum sodium levels
Mild	**130-135 meq/1**
Moderate	125-129meq/l
Severe	<125 meq/1

Treatment Strategy

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

1. Fluid restriction - defined as total fluid intake in 24 hrs equal to the volume of urine output of previous 24 hrs. It was advised in patients with SIADH.
2. Normal saline (0.9%) - given to hypovolemic patients.{eg. CSW }
3. Loop diuretic - given for excretion of free water in cases of SIADH .
4. 3% saline - in severe hyonatremic patients with neurological symptoms of hyponatremia.

Data Collection

For all patients clinical and demographic details, final diagnosis, investigations and management were recorded onto a standard data collection sheet as per the study proforma and later transferred to Microsoft excel spreadsheet for analysis.

Statistical Analysis

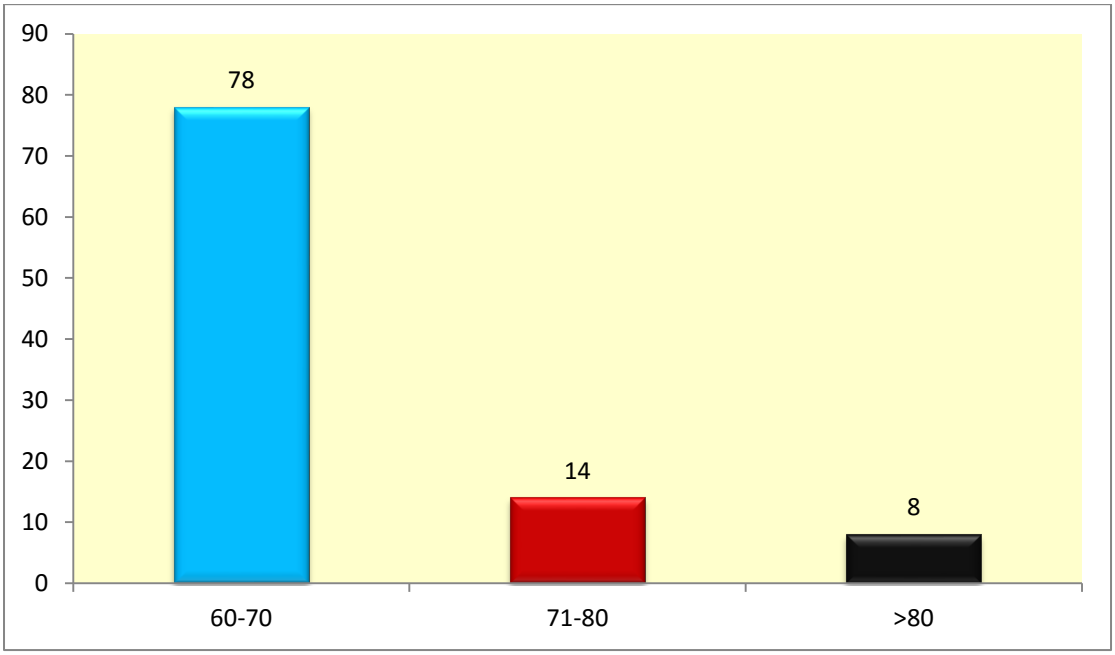
Analysis was done using SPSS for windows (version 20.0). Statistical method used was descriptive and analytical statistics. Data are presented as frequency distribution and simple percentages.Analysis were done using probability tests.

RESULTS

Table 8: Age-wise distribution

Age Group (years)	Number	Percentage
60-70	**39**	**78**
71-80	**7**	**14**
>80	**4**	**8**
Total	**50**	100

Graph 1: Age-wise distribution

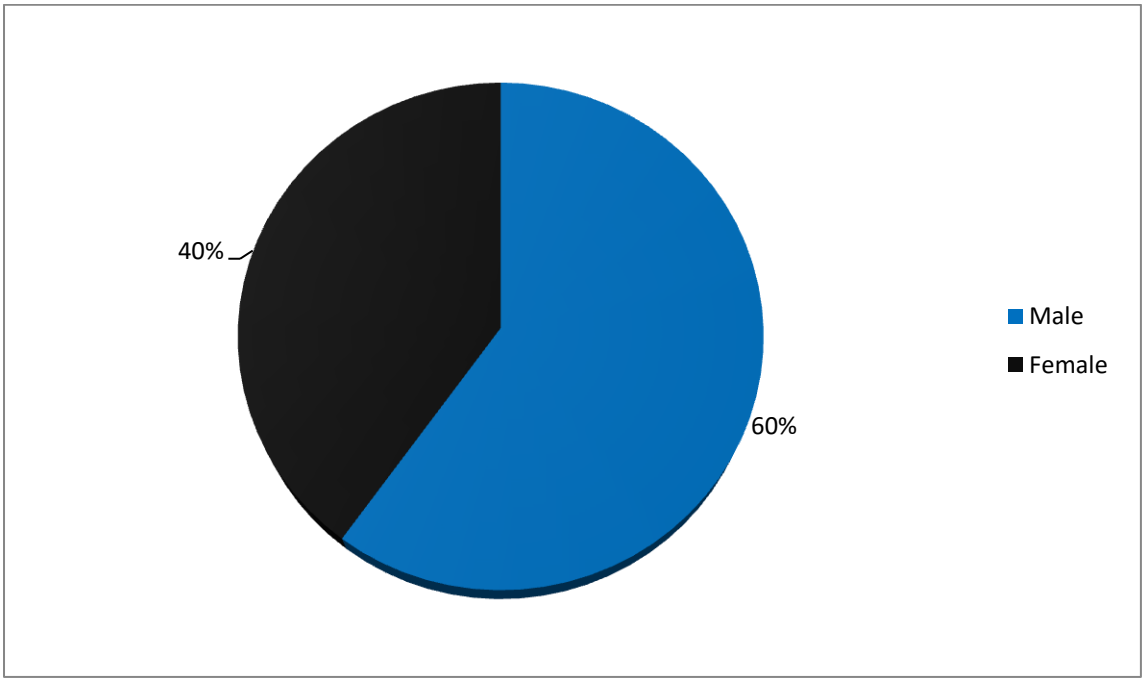


The maximum number of patients were in the age group 60-70 years, i.e. 39 cases (78%), 14% were in 71-80 group and 8% were in >80 group.

Table 9: Gender-wise distribution

Gender	Number	Percentage
Male	**30**	**60**
Female	**20**	**40**
Total	**50**	100

Graph 2: Gender-wise distribution

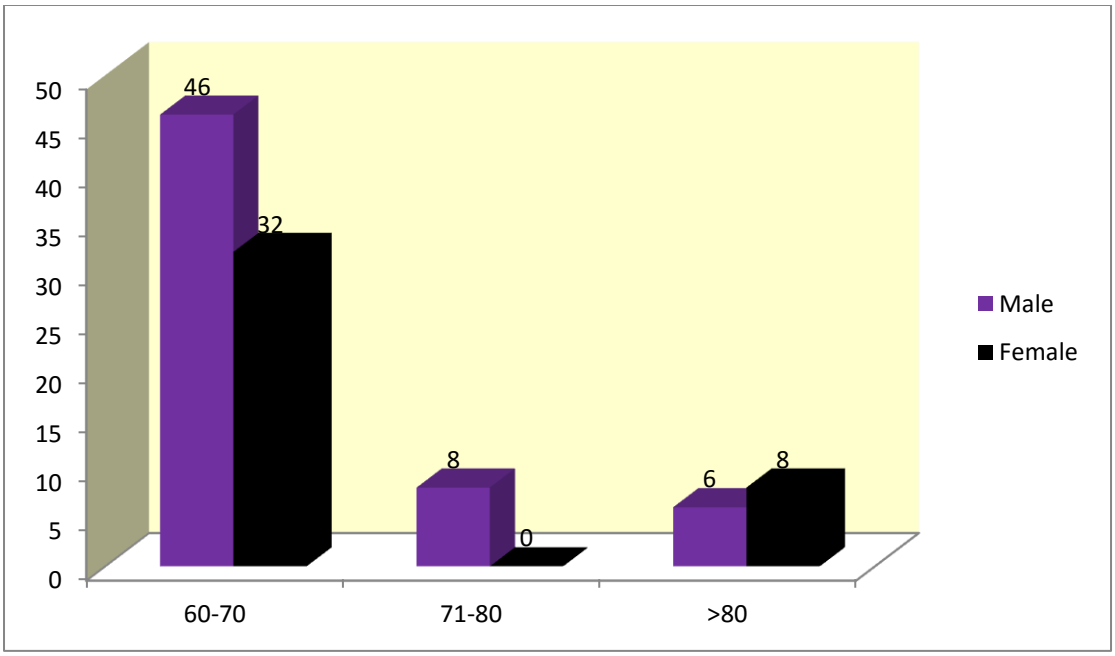


In the study out of 50,60% were males and 40% were females.

Table 10: Age and gender distribution

Age group (years)	Male		Female	
	Number	Percentage	Number	Percentage
60-70	**23**	**46**	**16**	**32**
71-80	**4**	**8**	**0**	**0**
>80	**3**	**6**	**4**	**8**
Total	**30**	**60**	**20**	**40**

Graph 3: Age and gender distribution



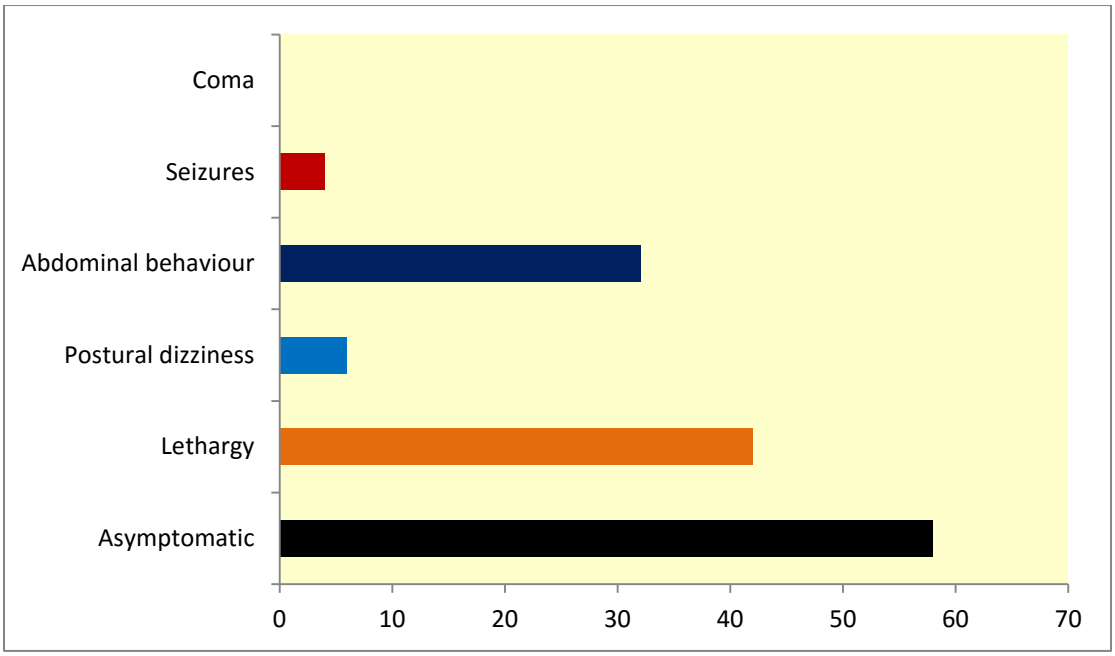
Out of the 30 males 23 falls in the age group of 60-70. Out of 20 females, 16 are

in the age group of 60-70. There were no females in the age group of 71-80 in the study.

Table 11: Symptomatology of hyponatremia

Symptoms	Number	Percentage
Asymptomatic	**29**	**58**
Lethargy	**21**	**42**
Postural dizziness	**3**	**6**
Abnormal behaviour	**16**	**32**
Seizures	**2**	**4**
Coma	**0**	**0**

Graph 4: Symptomatology of hyponatremia



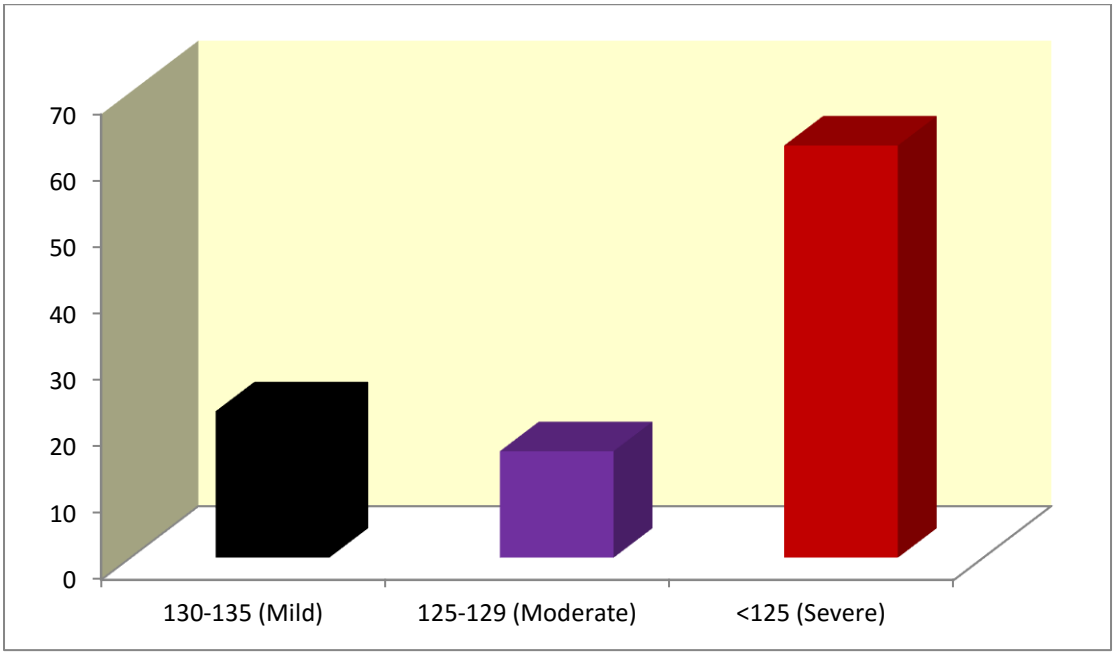
The majority of the cases were asymptomatic at time of presentation, 58%. Out the symptomatic cases, 42%, 100% had lethargy, 76% had abnormal

behaviour, 14% had postural dizziness and 9% (2 cases) had seizures. None of the patients were in coma.

Table 12: Severity of hyponatremia

Sodium levels (mmol/litre)	**Number**	**Percentage**
130-135 (Mild)	**11**	**22**
125-129 (Moderate)	**8**	**16**
<125 (Severe)	**31**	**62**
Total	**50**	**100**

Graph 5: Severity of hyponatremia



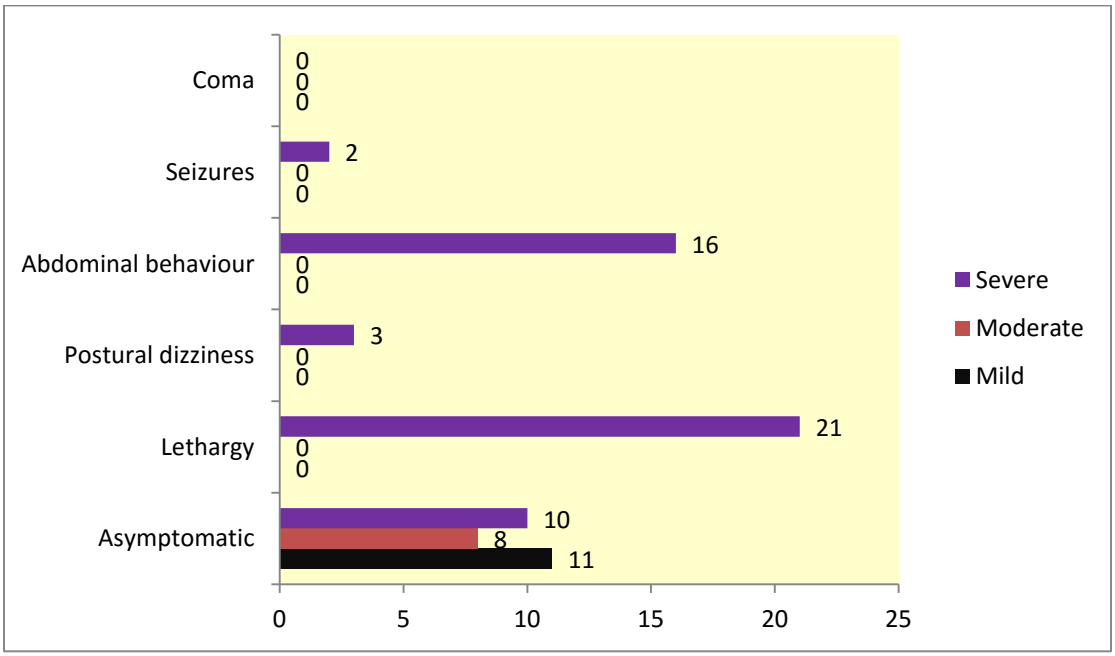
Out of 50 cases majority 62% were having severe hyponatremia, 16% were

having moderate hyponatremia and 22% were having mild hyponatremia.

Table 13: Correlation of symptoms with levels of hyponatremia

Symptoms	Mild	Moderate	Severe
Asymptomatic	**11**	**8**	**10**
Lethargy	**0**	**0**	**21**
Postural dizziness	**0**	**0**	**3**
Abdominal	**0**	**0**	**16**
Seizures	**0**	**0**	**2**
Coma	**0**	**0**	**0**

Graph 6: Correlation of symptoms with levels of hyponatremia

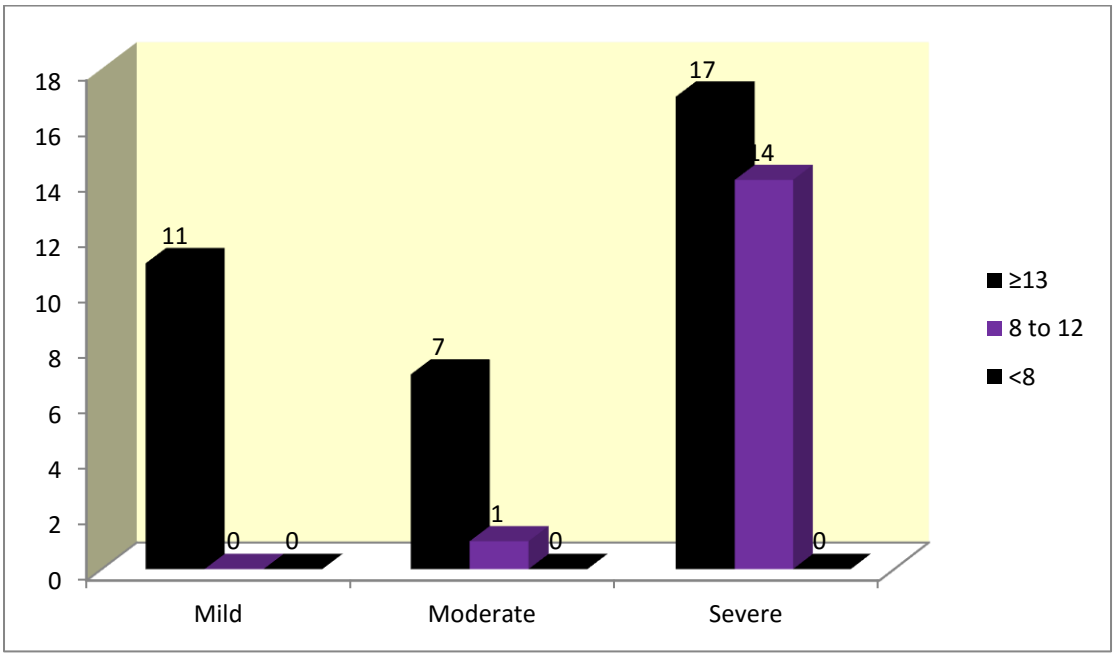


Out of 29 asymptomatic patients 11 were having mild hyponatremia, 10 were having severe hyponatremia and 8 were having moderate hyponatremia. All the symptomatic patients were having severe hyponatremia.

Table 14: GCS score and level of hyponatremia

Levels of hyponatremia	GCS score		
	≥13	8 to 12	<8
Mild	**11**	**0**	**0**
Moderate	**7**	**1**	**0**
Severe	**17**	**14**	**0**
Total	**35**	**15**	**0**

Graph 7: GCS score and level of hyponatremia

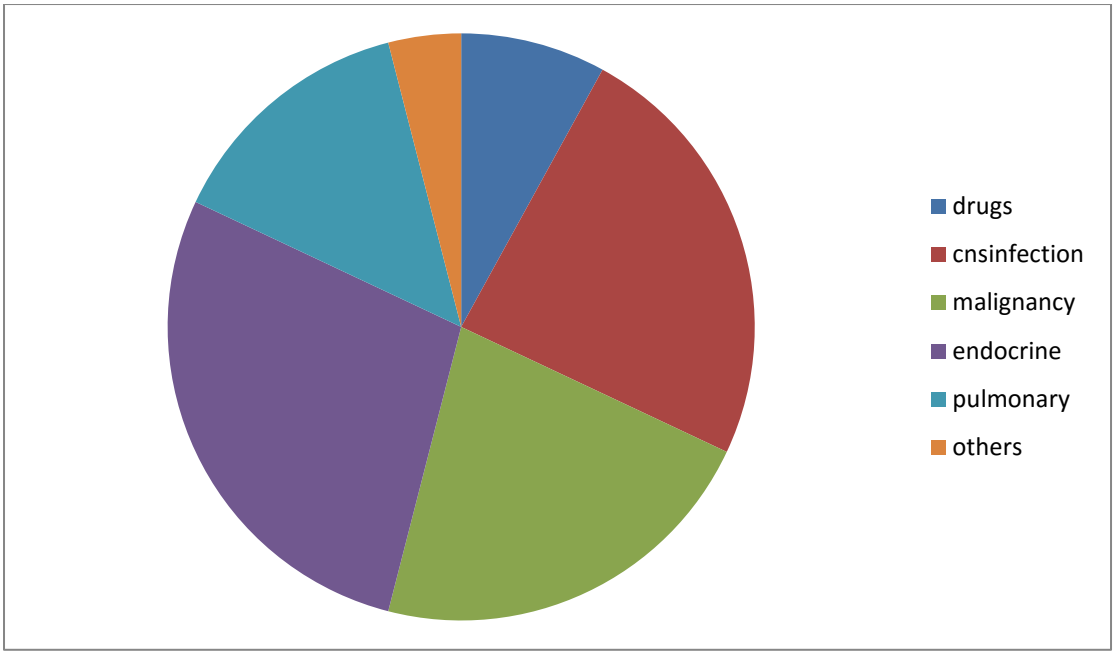


All the mild hyponatremic patients (11) had GCS≥13. Out of 8 moderate hyponatremic patients 7 had GCS≥13 and 1 had GCS 8-12. Out of 31 severe hyponatremic patients 17 had GCS≥13 and 14 had GCS 8-12. None of the patients hadGCS<8

Table 16: Predisposing factors

Predisposing factor	Number	Percentage
Drugs	4	8
Nonosmotic stimuli /others	2	4
Cns lesions	12	24
Malignancy	11	22
Endocrine Causes	14	28
Pulmonary Diseases	7	14

Graph8:Predisposingfactors



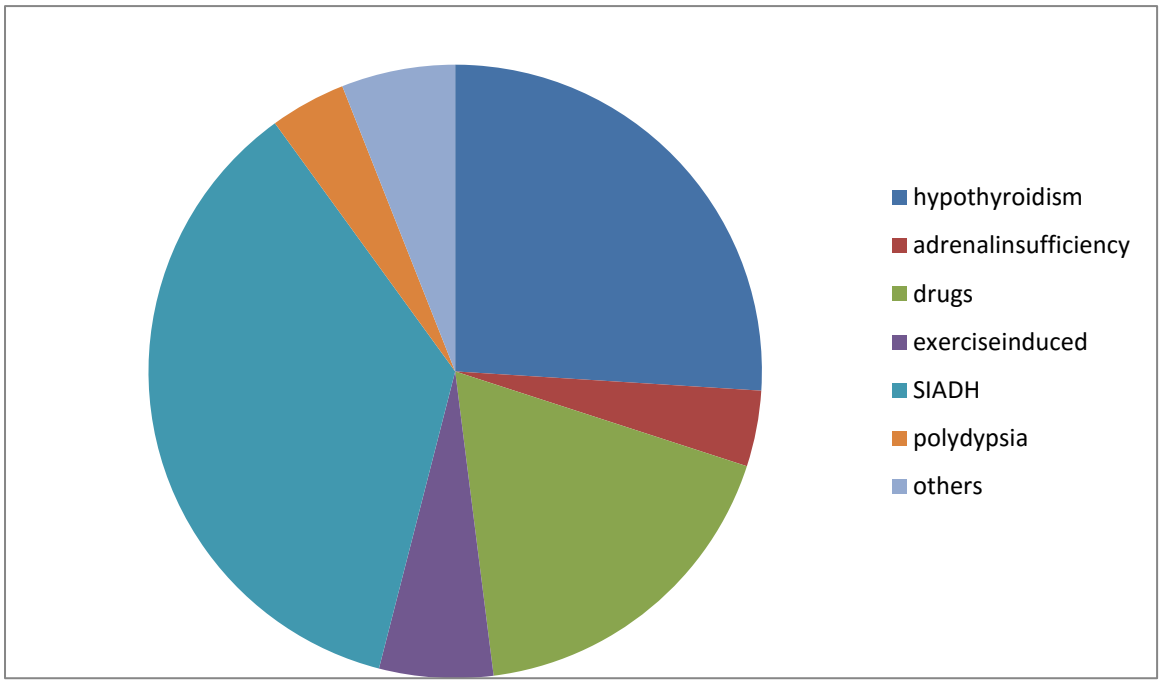
Cns infections and endocrine causes constitute the major predisposing

Factors ;followed by malignancy and pulmonary diseases

Table 17: Etiology of euvolemic hyponatremia

Etiology	Number	Percentage
Hypothyroidism	13	26
Adrenal insufficiency	2	4
Drugs	9	18
Exercise induced	3	6
SIADH	18	36
Primary polydipsia	2	4
Others	3	6

Graph 9: Etiology of euvolemic hyponatremia

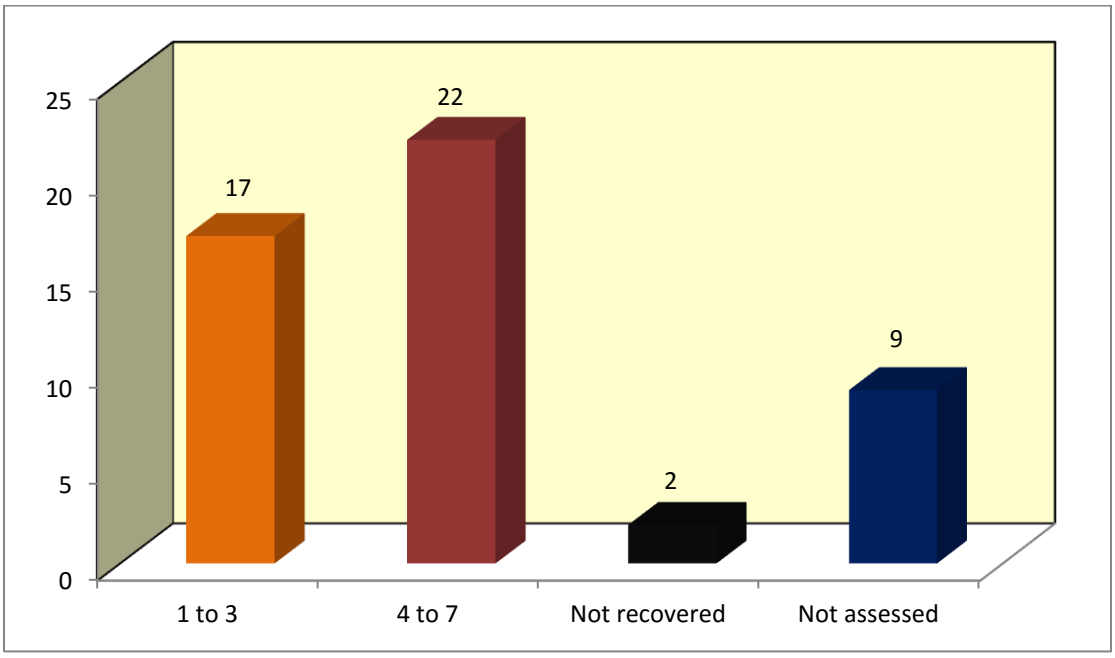


Out of 50 cases most common etiology was SIADH .About 36 % had SIADH.26% had hypothyroidism.18 % were having drug induced hyponatremia . 6 % with exercise induced, and other causes like reset osmostat.

Table 18: Outcome

Days for normalising sodium	Number
1 to3	17
4to7	22
Not recovered	2
Not assessed	9
Total	**50**

Graph 10: Outcome



The days for normalising sodium were noted during the study. For 17

cases, 1-3 days were needed, 22 cases needed 4-7 days. 2 cases had not recovered. One was a case of hypothyroidism and another case of SIADH with poor intake and vomiting. 9 cases were not assessed as 8 patients got discharged against medical advises and one patient died the next day of admission following IHD. No complications occurred due to treatment of hyponatremia.

Relation between serum sodium and other parameters

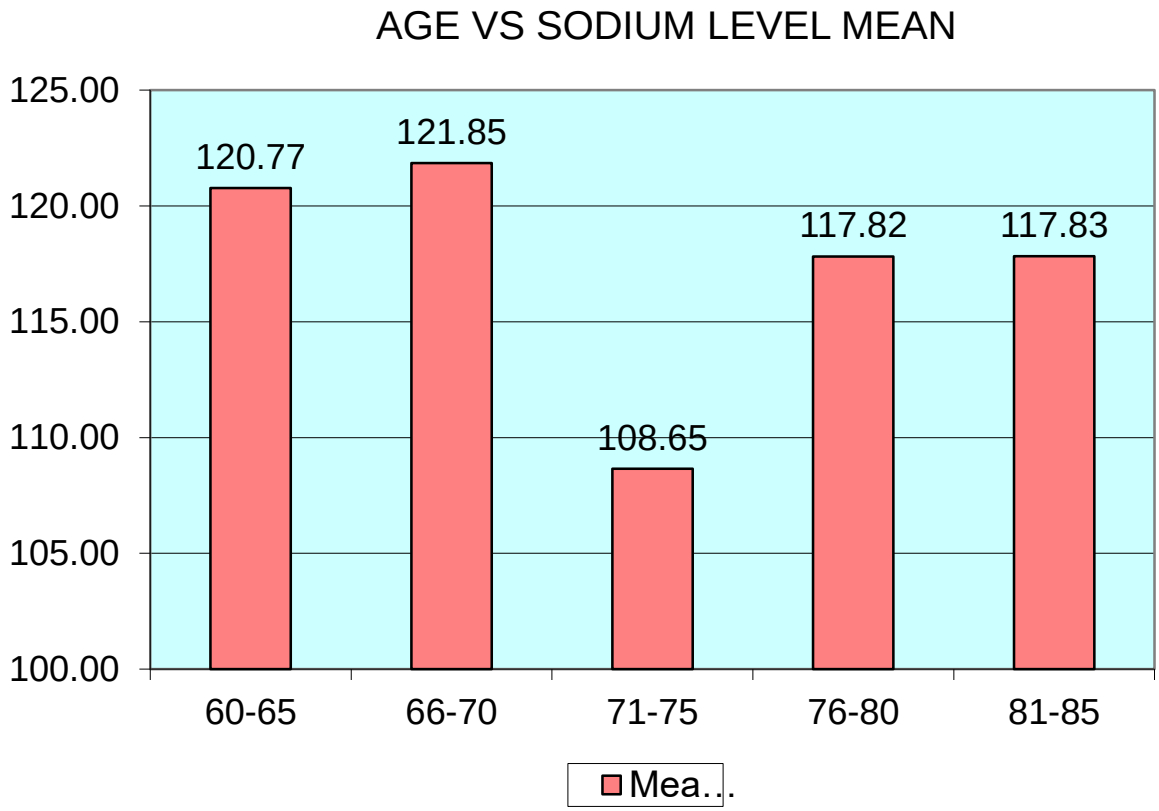
Association between serum sodium and age

Age	PATIENTS	Mean Na	SD
60-65	29	120.766	8.895
66-70	10	121.85	10.794
71-75	2	108.65	7.566
76-80	5	117.82	10.201
81-85	4	117.825	7.491
Total	50		
Overall Mean	67.08	119.968	9.321
Age vs Na	0.411 NS		

P value of 0.411 . no significant association with age and serum sodium level.

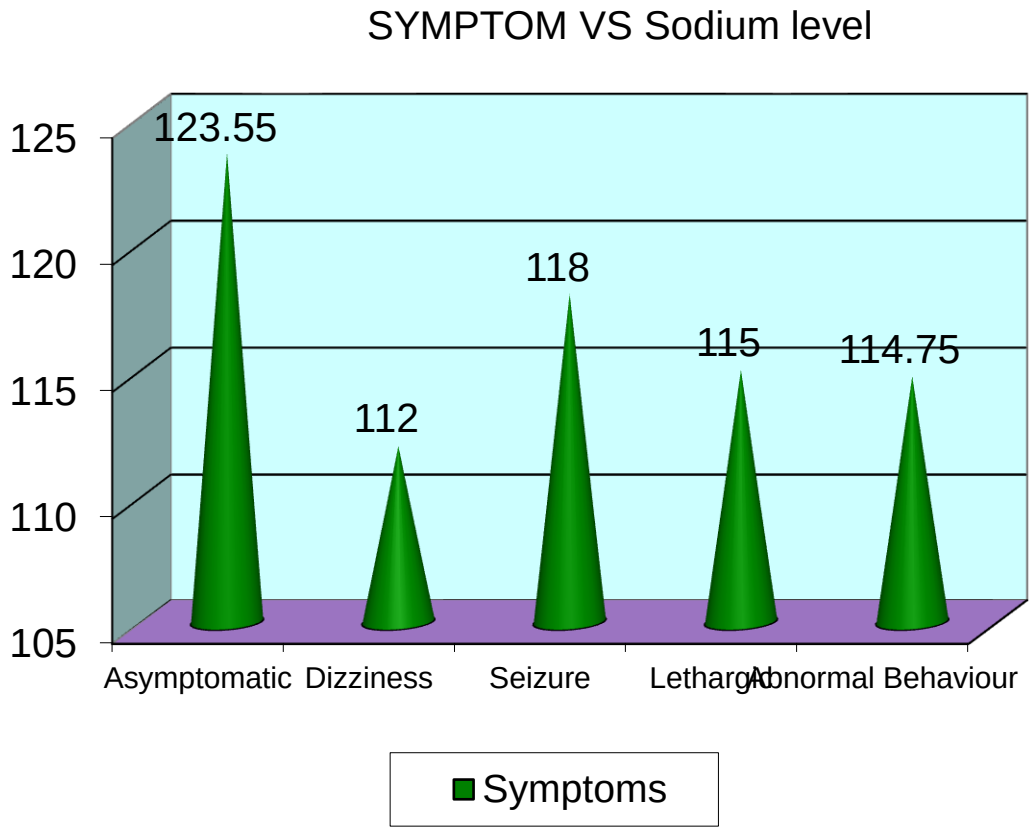
Mean age 67.08

Mean serum sodium 119.968 (s.d : 9.321)



Relation between serum sodium level and symptoms

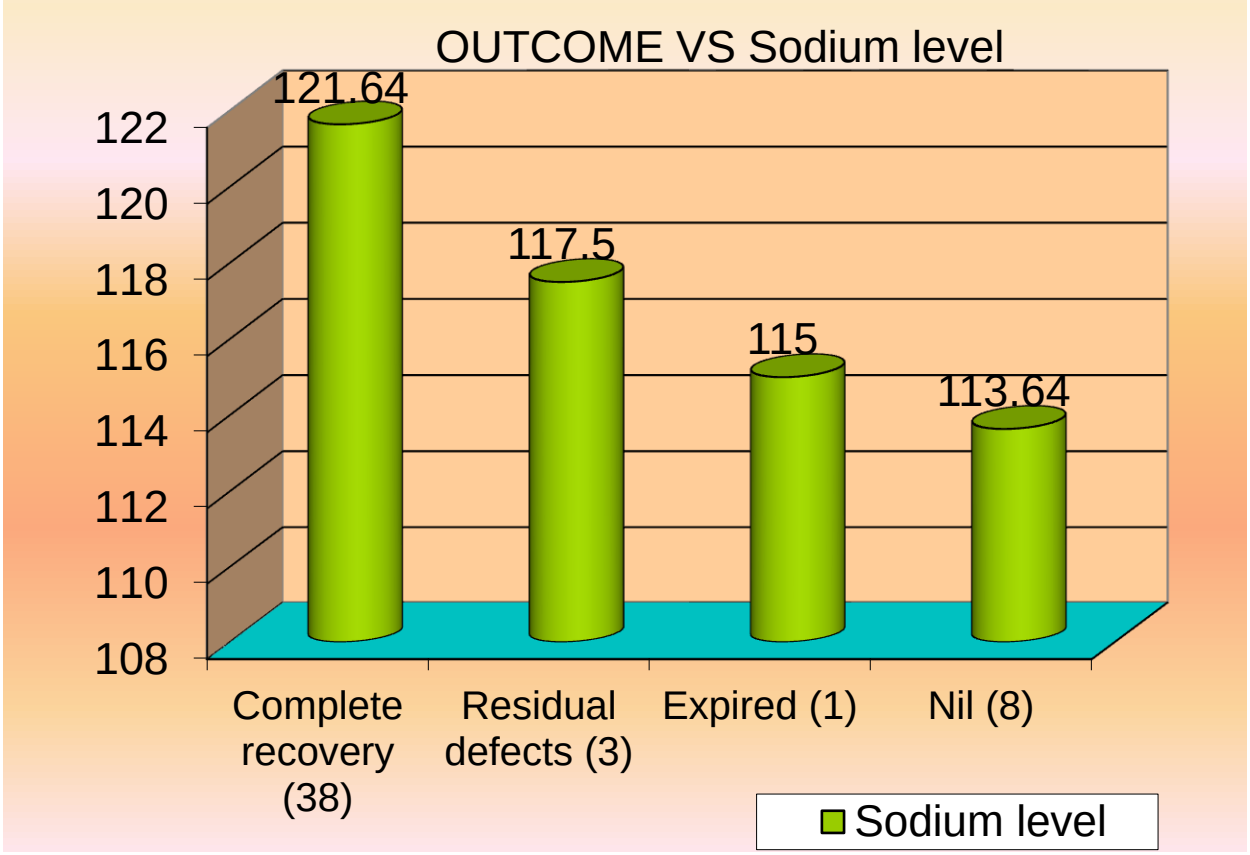
Symptoms	Sodium level	SD
Asymptomatic	123.55	8.971
Dizziness	112	9.849
Seizure	118	8.485
Lethargic	115	7.475
Abnormal Behaviour	114.75	7.688
p value	0.002 Sig	



There is significant association between serum sodium values and symptoms.

Relation between outcome and serum sodium levels

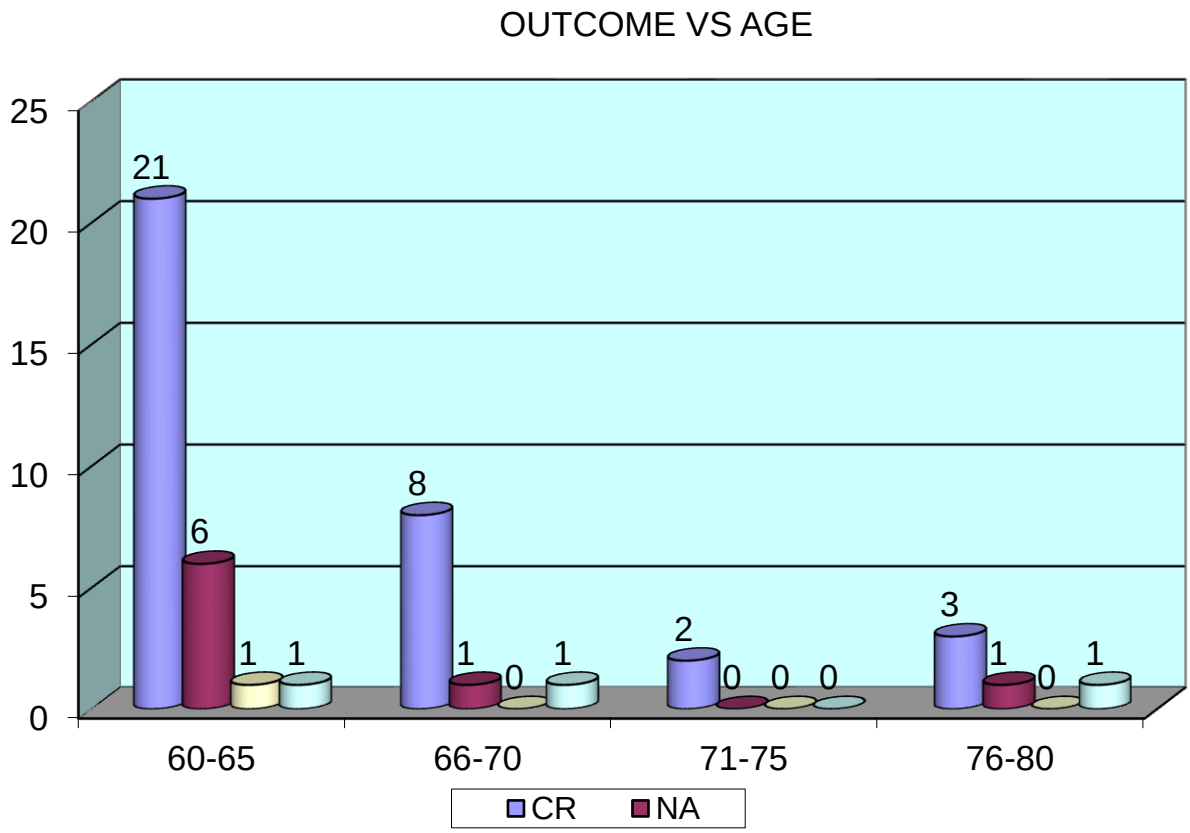
OUTCOME	Sodium level	SD
Complete recovery (38)	121.64	9.506
Residual defects (3)	117.5	5.766
Expired (1)	115	1
Nil (8)	113.64	7.272
p value (38/50 vs 12/50)	0.023 Sig	



p value of .023 ; there is significant association between serum sodium values and outcome.

Relation between age of the patient and outcome.

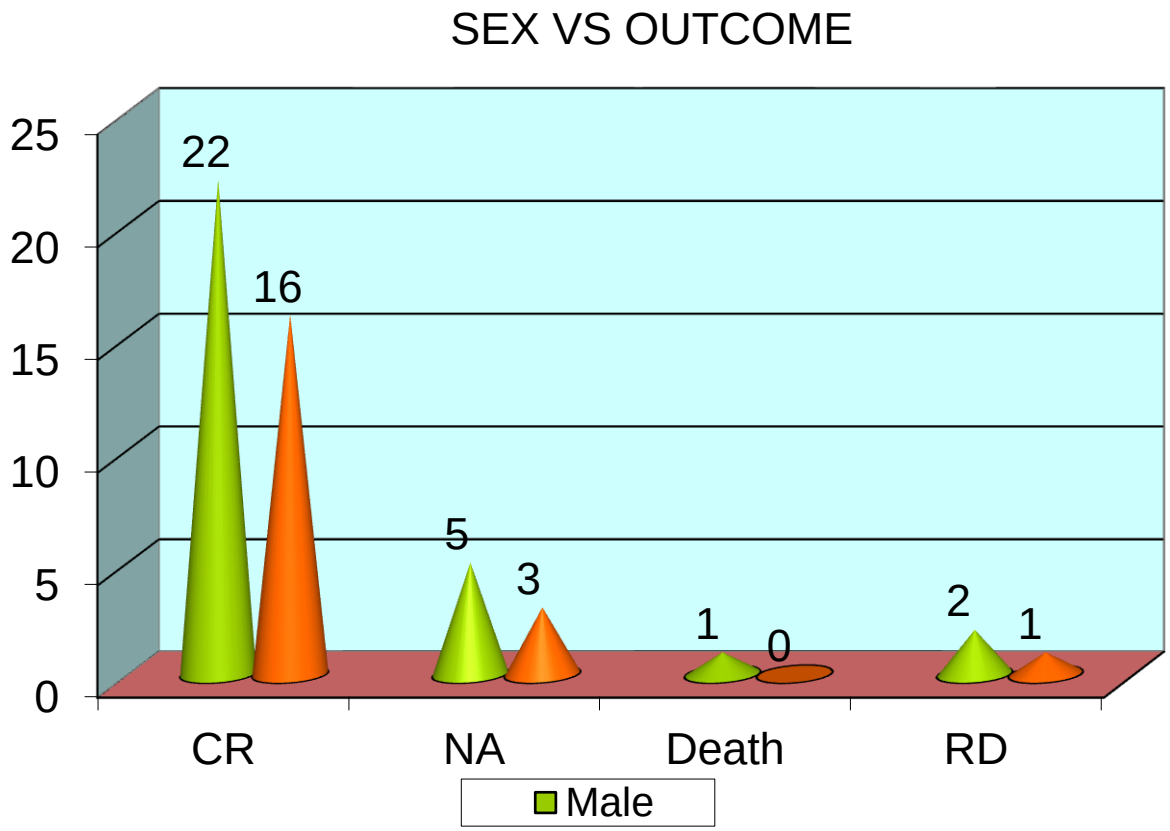
OUTCOME					
Age	**PATIENTS**	**CR**	**NA**	**Death**	**RD**
60-65	29	21	6	1	1
66-70	10	8	1	0	1
71-75	2	2	0	0	0
76-80	5	3	1	0	1
81-85	4	4	0	0	0
+Total	50	38	8	1	3



P value of .013 ,there is significant association between age of the patient and recovery.

Relation between sex of the patient and outcome.

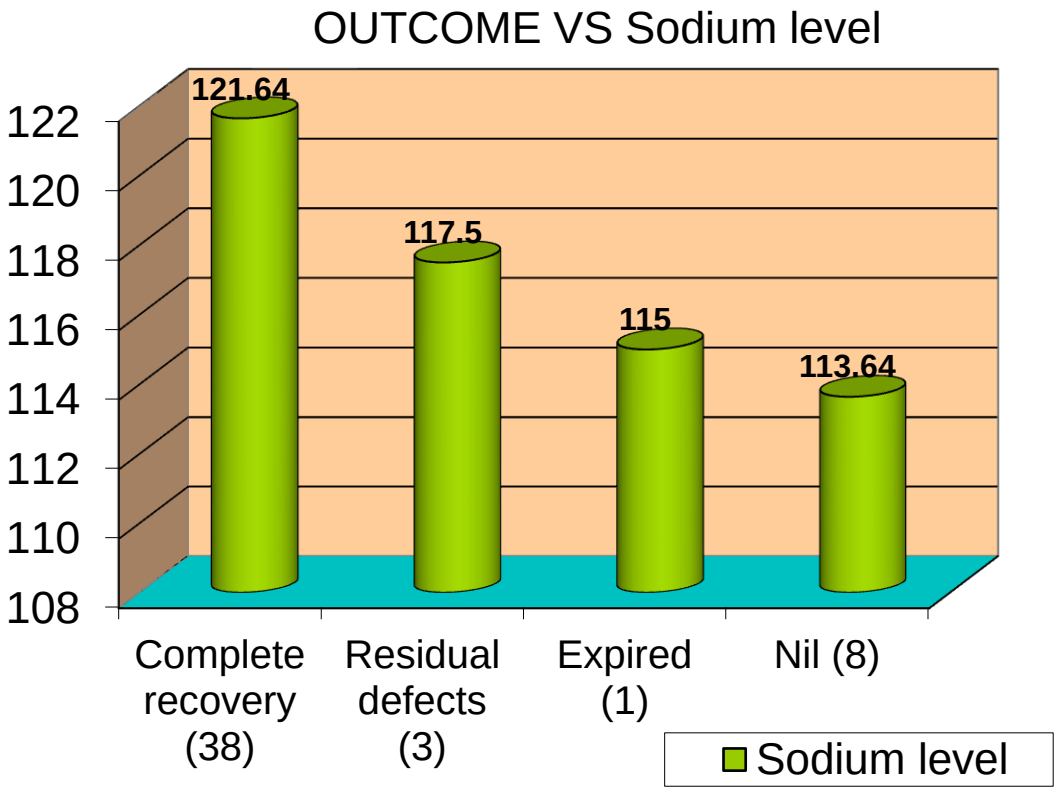
Final					
Sex	**PATIENTS**	**CR**	**NA**	**Death**	**RD**
Male	30	22	5	1	2
Female	20	16	3	0	1
Total	50	38	8	1	3



Pvalue – 0.551.There is no significant correlation between sex of the patient and outcome.

Relation between outcome and serum sodium levels

OUTCOME	Sodium level	SD
Complete recovery (38)	121.64	9.506
Residual defects (3)	117.5	5.766
Expired (1)	115	1
Nil (8)	113.64	7.272
p value (38/50 vs 12/50)	0.023 Sig	



There is significant association between serum sodium levels and outcome.(p value of 0.023)

DISCUSSION

This study was undertaken keeping in view of frequent occurrence of hyponatremia in the elderly sick patients who are at higher risk of development of electrolyte disturbance as these people have age related physiological changes in the function of kidneys and other multiple co-morbid conditions.

In the present study 50 elderly patients (≥60 years) were included. Out of 50, 60% (30) were males and 40% (20) were females.

In study done by Rao et al. 55 were females and 45 were male. In study by Mahavir et al. 64.3% were males and 53.7% were females. In study by Rubio et al. 52.7% were females and 47.3% were males. In study by Vurghese et al. males were 56.1%, females 43.9%

In the present study majority, 78%(39) of the cases were in the age group 60-70 years. 14% were in 71-80 group and only 8% were in > 80 group.

Out of the 30 males 23(46%) falls in the age group of 60-70. Out of 20 females 16(32%) are in the age group of 60-70. There were no females in the age group of 71-80 in the study.

The majority of the cases were asymptomatic at time of presentation, 58%. Out the symptomatic cases, 42%, 100%> had lethargy, 76% had abnormal behaviour, 14% had postural dizziness and 9% (2 cases) had seizures. Both the

patients had GTCS, had recovered when serum sodium normalised. None of the patients were in coma.

In study Rao et al., lethargy, drowsiness with slow response and irrelevant talk were the common presenting symptoms. 4% had seizures.

In study by Mahavir et al. confusion was present in 30% and altered sensorium in 17.1%. 2% had seizures. 14% were asymptomatic.

When hyponatremia develops more gradually,cerebral neurons have the time to respond by reducing the intracellular osmolality,through reduction in cell potassium and by reduced synthesis and efflux of intracellular organic osmolytes.The osmotic gradient favoring water movement into the cells is thus reduced , and patients may present with minimal or no symptomatology.

In the present study 62% had severe hyponatremia, 22% had moderate hyponatremia and 16% had mild hyponatremia. This could not be compared with other studies because the range of hyponatremia of mild, moderate and severe is different in this study.

In the present study out of 29 asymptomatic patients, 11 were having mild hyponatremia, 10 were having severe hyponatremia and 8 were having moderate hyponatremia. All the symptomatic patients were having severe hyponatremia.

When the GCS score was compared, all the mild hyponatremic patients (11) had GCS ≥13. Out of 8 moderate hyponatremic patients 7 had GCS ≥13, 1 had GCS 8-12. Out of 31 severe hyponatremic patients 17 had GCS≥ 13, 14 had

GCS 8-12. None of the patients had GCS <8.

In the study by Rao et al., 61% were euvolemic, 23% were overloaded and 16% dehydrated. The commonest type of hyponatremia noted in the study was euvolemic hypo-osmolar hyponatremia.

In the study by Miyashita et al. 95% had hypotonic hyponatremia out of which 63% had hypovolemia, 5% had hypervolemia and 32% euvolemia.

In the present study out of 50 patients, most common predisposing factor was endocrine causes followed by cns lesions followed by malignancy and pulmonary diseases

In the present study out of the cases most common etiology was SIADH, about 36% had SIADH.26% had hypothyroidism.18% having drug induced hyponatremia, 6% with exercise induced and other causes

In the study by Rao et al. common causes were SIADH (30%) followed by drugs (24%).

In study by Varghese et al. most common etiology was SIADH (34.8%), CKD (19.69%), CCF (18.18%), 6% of DM, HTN, cirrhosis and 3% acute gastroenteritis.

In the study by Mahavir et al. decreased intake (82.9%) was the most common etiology, increased loss (65.7%) was also present as second most common cause.

The days for normalising sodium were noted during the present study. For 17 cases 1-3 days were needed, 22 cases needed 4-7 days. 2 cases had not recovered. One was a case of hypothyroidism and another case of SIADH with poor intake and vomiting. 9 cases were not assessed as 8 patients got discharged against medical advise and one patient died the next day of admission following IHD. No complications occurred due to treatment of hyponatremia.

In study by Rao et al., 20 patients died secondary to hyponatremia

In study by Mahavir et al., time taken for recovery was 3.7±2.4 days. No mortality was observed.

In study by Rubios et al., in-hospital mortality due to hyponatremia was 12.9%.

In study by Chua et al. mean length of hospital stay was 13 days. Mortality rate was 8% out of 103 cases.

There is significant association between serum sodium levels and symptoms and with outcome of the patients.Also study found out association between age of the patient and outcome.In the study done by Rao et al indicate a higher mortality in the elderly patients with severe hyponatremia.

CONCLUSION

Hyponatremia is a common electrolyte abnormality found in hospitalised patients. It is more common in elderly patients.

Lethargy was the most common symptom. Other common symptoms were abnormal behaviour and postural dizziness. All the symptomatic cases had severe hyponatremia. There is significant association between serum sodium levels and symptoms and with outcome of the patients.Also study found out association between age of the patient and outcome.

Most common etiology was SIADH. Other major causes were hypothyroidism,drugs,exercise. 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 who are symptomatic. Treatment with hypertonic saline is safe provided gradual correction of hyponatremia is followed.

Osmotic demyelination 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.

A systematic approach to the diagnosis of hyponatremia with the

application of simple diagnostic algorithms, using history, clinical examination and laboratory findings to establish mechanism of hyponatremia can significantly improve the management and outcome of hyponatremia.

SUMMARY

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

The study was conducted in a tertiary care centre . Successive patients of hyponatremia were included in the study. These patients were evaluated for the underlying cause of hyponatremia which included detailed history and physical examination followed by appropriate laboratory investigations based on serum osmolality.

Fifty patients were included in the study. 58% were asymptomatic at time of presentation. Out of symptomatic cases 100% had lethargy, 76% had abnormal behaviour and 14% had postural dizziness. There was wide range of etiologies, most common being SIADH (36%). Hypertonic saline was given to 54%, fluid restriction was advised for 44%, 10% were given normal saline. One patient had died during the study, cause of death being IHD. No complications were reported during treatment of patients with hyponatremia. Treatment with hypertonic saline is safe provided gradual correction of hyponatremia is followed.

There is significant association between serum sodium levels and

symptoms and with outcome of the patients.Also study found out association between age of the patient and outcome.

Osmotic demyelination 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.

Hyponatremia is a common problem in hospitalised patients. The possible cause of hyponatremia should always be determined, as outcome in severe hyponatremia is governed by etiology and not by serum sodium level. The correction of hyponatremia also helps to improve the prognosis of the underlying disease and helps to prevent further complications due to the hyponatremia itself.

LIMITATIONS OF THE STUDY

1. Smaller study group
2. Only short term mortality and morbidity are assessed. Long term morbidity in the form of re-admission and long term mortality are not assessed.
3. Male to female ratio was not similar to most of other studies.
4. The etiology of hyponatremia in older people is predominantly multifactorial, with patients presenting with doubtful signs of hydration.
5. In the present study 62% had severe hyponatremia, 22% had moderate hyponatremia and 16% had mild hyponatremia. This could not be compared with other studies because the range of hyponatremia of mild, moderate and severe is different in this study.
6. The study population involved patients seeking medical care in a tertiary care centre and hence may not represent the general population.

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LIST OF ABBREVIATIONS

ACE	→	Angiotensin converting enzyme
ADH	→	Anti diuretic hormone
ANP	→	Atrial natriuretic peptide
APUD	→	Amine precursor uptake and decarboxylating
AVP	→	Arginine vasopressin
BNP	→	Brain natriuretic peptide
BUN	→	Blood urea nitrogen
CBC	→	Complete blood count
CCF	→	Congestive cardiac failure
CHF	→	Congestive heart failure
CKD	→	Chronic kidney disease
CLD	→	Chronic liver disease
CNS	→	Central nervous system
CPM	→	Central pontine myelinolysis
CSF	→	Cerebro spinal fluid
CSW	→	Cerebral salt wasting
CVA	→	Cerebrovascular accident
D5W	→	5% dextrose
DC	→	Differential count
DM	→	Diabetes mellitus
EAH	→	Exercise associated hyponatremia
ECF	→	Extra cellular fluid
ECV	→	Effective circulating volume
GCS	→	Glasgow Coma Scale
GFR	→	Glomerular filtration rate

GTCS	→	Generalised tonic clonic seizures
Hb	→	Haemoglobin
HCO_3	→	Bicarbonate ion
HIV	→	Human immune deficiency virus
HTN	→	Hypertension
ICF	→	Intra cellular fluid
IHD	→	Ischaemic heart disease
ISE	→	Ion selective electrode
JVP	→	Jugular venous pulse
K^+	→	Potassium ion
MAOI	→	Mono amine oxidase inhibitors
MDMA	→	3,4-methylene dioxy meth amphetamine
MRI	→	Magnetic resonance imaging
Na^+	→	Sodium ion
NSAID	→	Non-steroidal anti inflammatory drug
Pit	→	Platelet
RAA	→	Renin angiotensin aldosterone
SIADH	→	Syndrome of inappropriate anti diuretic hormone
SSRI	→	Selective serotonin re-uptake inhibitors
TB	→	Tuberculosis
TBW	→	Total body water
TCA	→	Tri cyclic anti depressants
TLC	→	Total leucocyte count
TRH	→	Thyrotropin releasing hormone
TURP	→	Trans urethral resection of prostrate
URE	→	Urine routine examination

PROFORMA

CASE NO.

NAME:

AGE:

SEX:

ADDRESS:

CHIEF COMPLAINTS

HISTORY OF PRESENT ILLNESS

PAST HISTORY

FAMILY HISTORY

PERSONAL HISTORY

PROVISIONAL DIAGNOSIS

CLINICAL EXAMINATION

P.R.

B.P.

RESPIRATORY RATE

PALLOR-YES/NO

ICTERUS-YES/NO

OEDEMA-YES/NO

SKIN TURGOR AND ORAL CAVITY: NORMAL/MILD DEHYDRATION/
MARKED DEHYDRATION

SIGNS OF PERIPHERAL CIRCULATORY FAILURE: YES/NO

GOITRE: YES/NO

SIGNS OF HYPOTHYROIDISM: YES/NO

CNS EXAMINATION

CONSCIOUS/ABNORMAL BEHAVIOUR/DROWSY/STUPOR/COMA

CRANIAL NERVE DEFICITS-YES/NO

MOTOR SYSTEM

DTJ- NORMAL/BRISK/DEPRESSED

PLANTARS: FLEXOR/EXTENSOR/MUTE

GAIT ATAXIA: YES/NO

CEREBELLAR SIGNS: PRESENT/ABSENT

GCS:/15

RESPIRATORY:

CVS:

ABDOMEN:

PROFILE OF INVESTIGATIONS

Hb(g/dl)

TLC

DLC

Plt count

$S.Na^{+}$

$S.K^{+}$

s.cr

BUN

S.Creatinine

RBS

Total Protein

S. albumin

S. cholesterol

S.LDL

FINAL DIAGNOSIS

PREDISPOSING FACTOR

DIURETIC USE: YES /NO

VOMITING: YES/NO

SWEATING: YES/NO

CNS INFECTION/SURGERY: YES/NO

POOR INTAKE: YES /NO

DIARRHOEA: YES/NO

HYPOTONIC FLUID USE: YES/NO

PULMONARY DISEASE: YES /NO

SYMPTOMS PERTAINING TO HYPONATREMIA

ASYMPTOMATIC: YES/NO

POSTURAL DIZZINESS: YES/NO

SEIZURES: YES/NO

LETHARGY: YES/NO

ABNORMAL BEHAVIOUR: YES/ NO

COMA: YES/NO

PRE-EXISTING ILLNESS

DIABETES: YES/NO

CHRONIC LIVER DISEASE: YES/NO

CONGESTIVE HEART FAILURE: YES/NO

HYPERTENSION: YES/NO

CKD: YES/NO

HYPOTHYROIDISM: YES/NO

COURSE IN HOSPITAL:

SPECIFIC INVESTIGATIONS

Plasma osmolality

Urine RE

Urine sp. Gravity

Urine osmolality

Urine Na^+

Urine K^+

TREATMENT GIVEN IN HOSPITAL

MANAGEMENT DETAILS

0.9% SALINE

3.0% SALINE

DIURETICS

WATER RESTRICTION

POTASSIUM REPLACEMENT

DURATION FOR NORMALISATION OF S.Na^+

DURATION FOR CLINICAL RECOVERY

COMPLICATIONS DURING THERAPY

RECURRENCE OF HYPONATREMIA

LIKELY CAUSE OF RECURRENCE

FINAL OUTCOME: COMPLETE RECOVERY/ RESIDUAL DEFICITS/DEATH

KEY TO MASTER CHART

ABD	→	Abdomen
ABN	→	Abnormal
ABN BE	→	Abnormal behaviour
ALB	→	Albumin
ASY	→	Asymptomatic
BBC	→	Bilateral basal creps
BP	→	Blood pressure
BUN	→	Blood urea nitrogen
C	-	Crepitations
CCF	→	Congestive cardiac failure
CKD	→	Chronic kidney disease
CL	→	Chloride
CLD	→	Chronic liver disease
CND	→	Cranial nerve deficits
CNSI/S	→	CNS infection/surgery
COM	→	Complication
Cr	→	Creatinine
CR	→	Complete recovery
CS	→	Cerebellar signs
Csl	-	serum cortisol
CVS	→	Cardiovascular system
CYN	→	Cyanosis
D	→	Drowsy
DEP	→	Depressed
DHY	→	Dehydration
DIA	→	Diarrhoea
DIZZ	→	Dizziness
DM	→	Diabetes mellitus
DNN	→	Duration of normalising sodium
DTJ	→	Deep tendon reflexes
E	→	Extensor

F → Female

Fl → Flexor

FLU → Fluid

GA → Gait ataxia

GALL → Gallop

GCS → Glasgow coma score

HEP → Hepatomegaly

HFU → Hypotonic fluid use

HTN → Hypertension

HYPO → Hypothyroidism

ICT → Icterus

K → Potassium

KR → Potassium replacement

LDL → Low density lipoprotein

LETH → Lethargy

LOC → Level of consciousness

M → Male

Mu → Mute

N → No

Na → Sodium

NA → Not assessed

NAD → No abnormality detected

NOR → Normal

NR → Not recovered

NS → Normal saline

OED → Oedema

PAL → Pallor

PC → Pus cell

Pl.Osm → Plasma osmolality

PLANT → Plantar

POI → Poor intake

PR → Pulse rate

PUL D/S	→	Pulmonary disease
RBS	→	Random blood sugar
RD	→	Residual deficit
REC	→	Recurrence
RES	→	Respiratory
RHON	→	Rhonchi
RR	→	Respiratory rate
S.Choi	→	Serum cholesterol
SEI	→	Seizures
SUG	→	Sugar
SWE	→	Sweating
T.Pro	→	Total protein
TSH	-	Thyroid stimulating hormone
U.Na	→	Urine sodium
U.Osm	→	Urine osmolality
URE	→	Urine routine examination
VOM	→	Vomiting
WR	→	Water restriction
Y	→	Yes
3%	→	3% saline