HYPONATREMIA AS AN INDEPENDENT PROGNOSTIC FACTOR FOR MORBIDITY AND MORTALITY IN EUVOLEMIC ICU PATIENTS

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled " **HYPONATREMIA AS AN INDEPENDENT PROGNOSTIC FACTOR FOR MORBIDITY AND MORTALITY IN EUVOLEMIC ICU PATIENTS** is the bonafide work of **Dr.L.MAHENDRAN**, in partial fulfilment 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 2019.

Dr.D.MARUTHU PANDIYAN ***M.S, FICS, FRCS***

THE DEAN,

Madurai Medical College,

Madurai.

CERTIFICATE FROM THE HOD

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PROF. DR. V.T. PREMKUMAR M.D.,
Professor and HOD,
Department Of Medicine,
Government Rajaji Hospital,
Madurai Medical College, Madurai.

CERTIFICATE FROM THE GUIDE

This is to certify that this dissertation entitled **"HYPONATREMIA AS AN INDEPENDENT PROGNOSTIC FACTOR FOR MORBIDITY AND MORTALITY IN EUVOLEMIC ICU PATIENTS** is the bonafide work of **Dr.L.MAHENDRAN**, in partial fulfilment 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 2019.

DR. S.RAVINDRAN M.D,
Professor of Medicine,
Chief VIIth Medical unit,
Madurai Medical College & Govt. Rajaji Hospital,
Madurai .

DECLARATION

I, **Dr.L.MAHENDRAN,** solemnly declare that, this dissertation titled - "**HYPONATREMIA AS AN INDEPENDENT PROGNOSTIC FACTOR FOR MORBIDITY AND MORTALITY IN EUVOLEMIC ICU 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.S.RAVINDRAN 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 fulfilment of the rules and regulations for the award of M.D Degree General Medicine Branch- I examination to be held in April 2019.

Place;Madurai Dr.L.MAHENDRAN.

Date;

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CONTENTS

BIBLIOGRAPHY

MASTER CHART

INTRODUCTION

- Hyponatremia is defined as serum sodium concentration less than 135 meq/l,

- Hyponatremia is the commonest electrolytes disturbance seen in hospitalized patients,
- The presence of hyponatremia worsen the prognosis in icu patients,

- Early recognition of hyponatremia and appropriate intervention would improve the outcome.

Low plasma sodium represents a relative water excess in conjunction with,impaired ability of the kidney to excrete electrolyte free water. Removal of excess water by the kidney requires urinary dilution, which is compromised in all patients in the ICU,

Primarily Hyponatremia, is due to imbalance in water homeostasis, antidiuretic hormone (ADH) regulation, and renal handling of filtered sodium.

Sepsis, shock, and multiple organ dysfunction syndrome, impair glomerular filtration, and enhance sodium and water reabsorption at the proximal tubule, thereby diminishing delivery of the filtrate to the diluting segment.

-Tubulointerstitial pathology reduce the reabsorption of sodium ,chloride in the diluting segment.

- Non osmotic stimuli for vasopressin production, like pain, nausea, medications, and hypovolemia lead to increased water reabsorption in the collecting duct.

- In the critical care setting; Inappropriate administration of hypotonic fluid also leads to Hyponatremia

-The clinical presentation of hyponatremia ranges from mild nonspecific symptoms, such as nausea, headache, and lethargy to severe neurological symptoms ,such as seizure and coma.

-Hyponatremic patients have longer ICU stay,longer mechanical ventilation days, higher morbidity and mortality.

* Timely diagnosis and treatment are the key to improve the clinical status ,and reduce the morbidity and mortality

AIMS AND OBJECTIVES

- To study the morbidity and mortality of icu patients who are having Euvolemic hyponatremia
- Hyponatremia is an independent prognostic factor to assess the outcome of Euvolemic icu patient

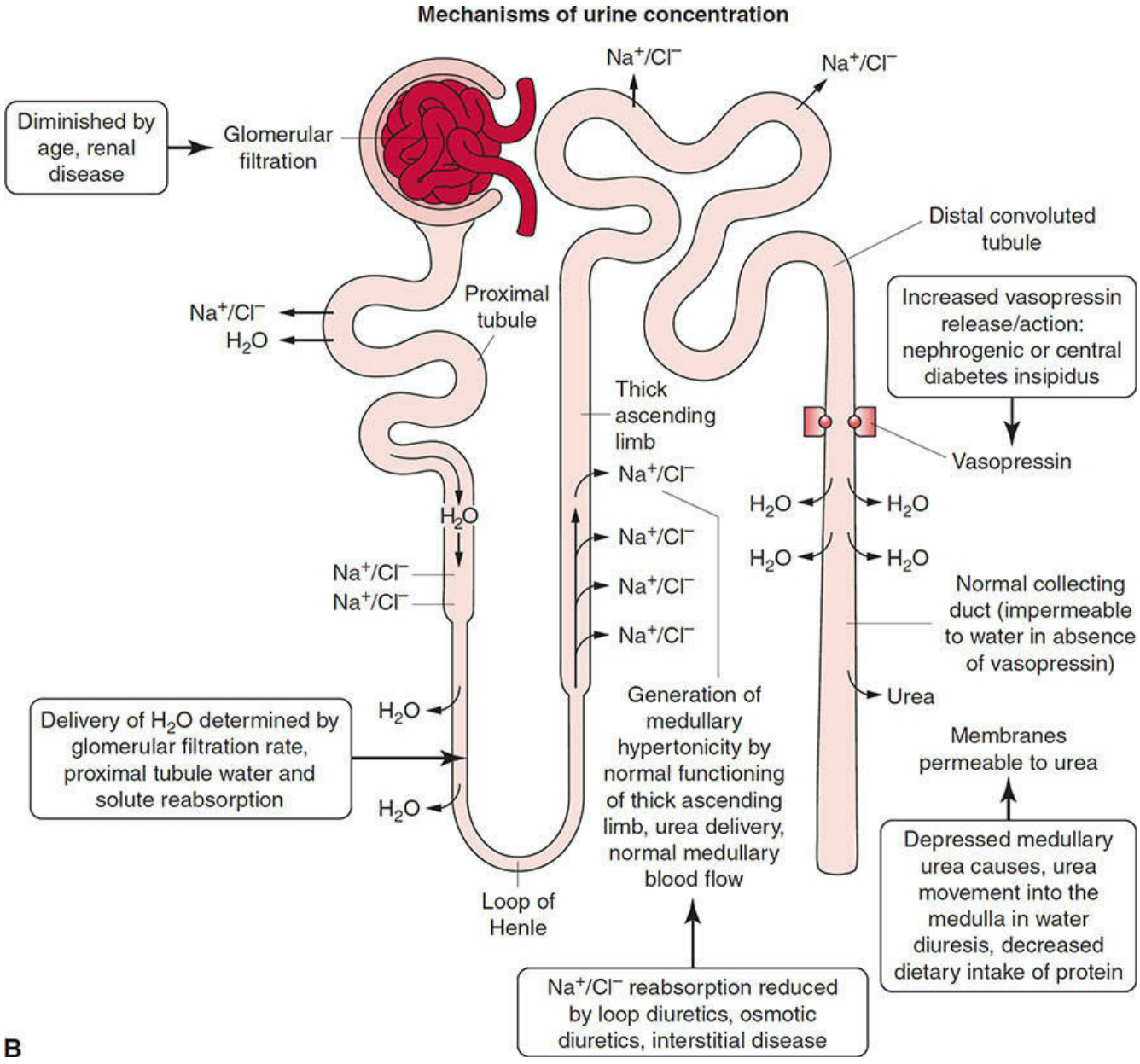
REVIEW OF LITERATURE

SODIUM AND WATER HOMEOSTASIS

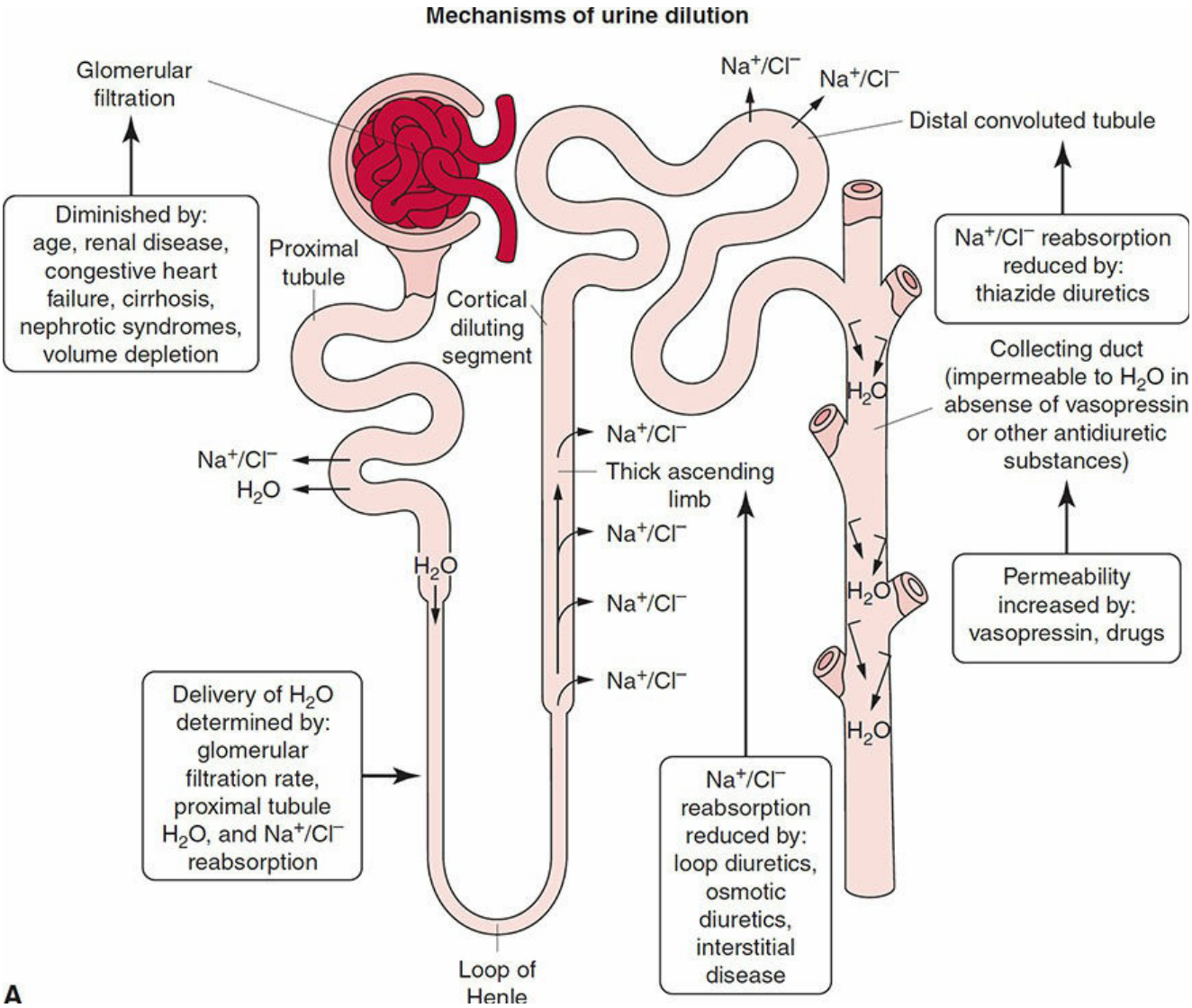
Any disturbances in the capacity of the kidney to concentrate and dilute the urine are central to the pathogenesis of disorders of water balance. These are depicted in Figure 1and 2 respectively, .The final excreted urine is hypotonic or hypertonic to plasma.

Renal concentrating capacity may be associated with water depletion, hypernatremia.Disorders of renal diluting capacity most frequently present with hyponatremia. Sodium and its accompanying anions, account for nearly all the osmotic activity of plasma .

Mechanisms of urine concentration



Mechanisms of urine dilution



Glomerular Filtration Rate and Proximal Tubular Reabsorption

The rates of glomerular filtration and proximal tubular reabsorption are Important in determining the rate of sodium and water delivery to the more distal portions of the nephron where the renal concentrating and diluting mechanisms are operative. Fluid reabsorption in the proximal tubule is isosmotic,So tubular fluid is neither concentrated nor diluted in the proximal portion of the nephron.

70% of glomerular filtrate is reabsorbed in the proximal tubules, the remaining 30% of fluid entering the loop of Henle , isotonic to plasma. The reabsorption of sodium chloride is primarily driven by the Na/H 3 transporter whereas the isotonic removal of water is facilitated by the expression of the water channel aquaporin 1 ,AQP1.

A decrease in glomerular filtration rate, or an increase in proximal tubular reabsorption, or both, may diminish the amount of fluid delivered to the distal nephron, and limit the renal capacity to excrete water. Diminished GFR and increased proximal tubular reabsorption may limit the delivery of sodium chloride to the ascending limb.

where the tubular transport of these ions without water initiates the formation of the hypertonic medullary interstitium. With diminished delivery of sodium chloride to the ascending limb, the resultant lowering of medullary hypertonicity impairs maximal renal concentrating capacity.

Descending and Ascending Limbs of the Loops of Henle, Distal Tubule, and Collecting Ducts:

Both the thin ascending limb in the inner medulla and the thick ascending limb in the outer medulla as well as the first part of the distal tubule, are impermeable to water as indicated by the thickened lining.

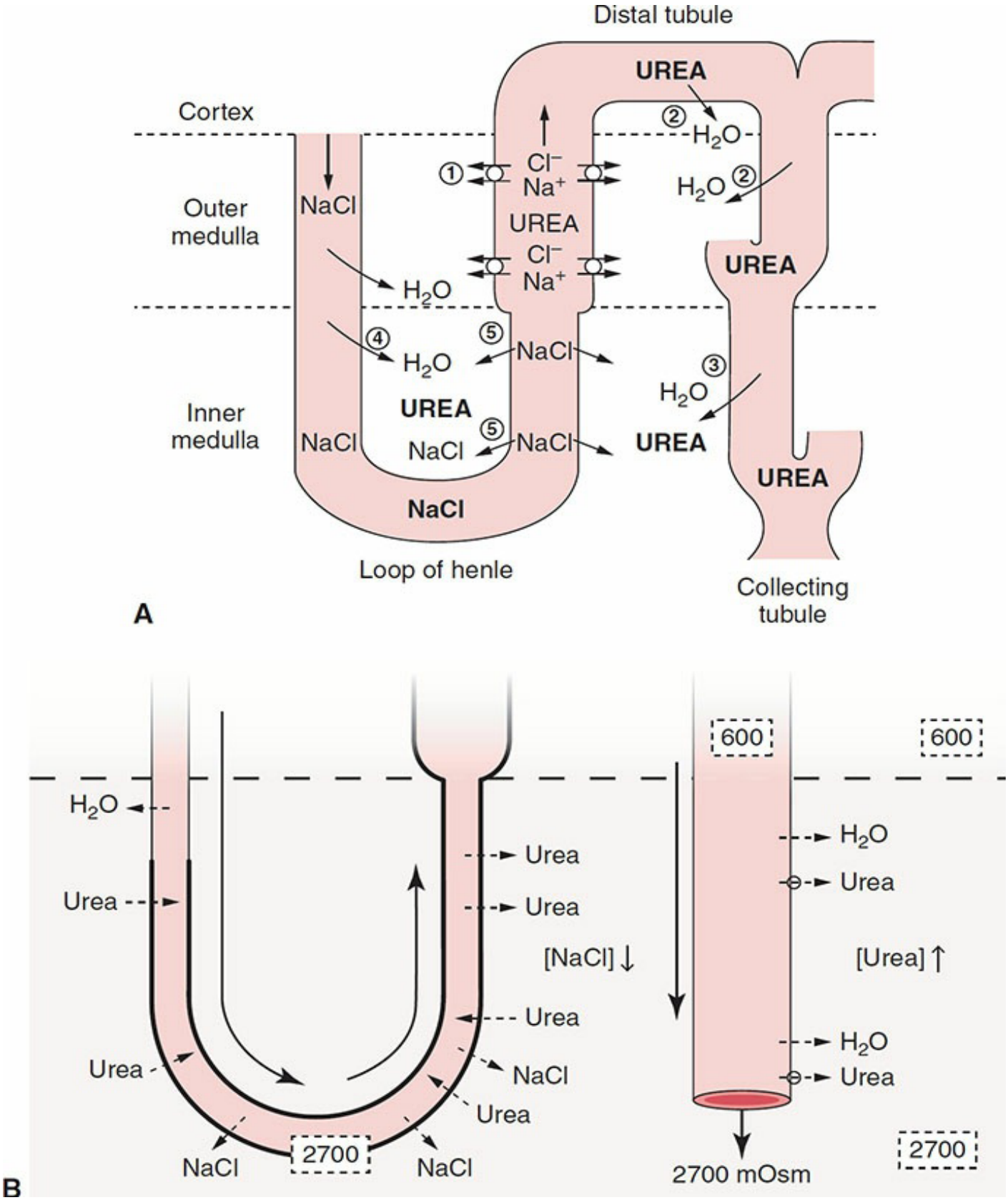
1. In the thick ascending limb, active sodium, chloride, and potassium cotransport renders the tubule fluid dilute and the outer medullary interstitium hyperosmotic

2. In the last part of the distal tubule and the collecting tubule in the cortex and outer medulla, water is reabsorbed down its osmotic gradient .

3. Increasing the concentration of urea that remains behind. In the inner medulla, both water and urea are reabsorbed from the collecting duct .

4. Some urea reenters the loop of Henle , This medullary recycling of urea, in
5. Addition to trapping of urea by countercurrent exchange in the vasa recta causes urea to accumulate in large quantities in the medullary interstitium where it osmotically extracts water from the descending limb and thereby concentrates sodium chloride in descending limb fluid.

6. When the fluid rich in sodium chloride enters the sodium chloride-permeable ,but water-impermeable thin ascending limb, sodium chloride moves passively down its concentration gradient rendering the tubule fluid relatively hyposmotic to the surrounding interstitium.


Distal tubule
UREA
Cortex
② H2O
Cl⁻
① Na⁺
H2O ②
Outer medulla
NaCl
UREA
Cl⁻
Na⁺
UREA
H2O
④ H2O
⑤ NaCl
③ H2O
Inner medulla
UREA
NaCl
⑤ NaCl
NaCl
NaCl
UREA
UREA
Loop of henle
Collecting tubule
A
600
600
H2O
Urea
Urea
Urea
[NaCl] ↓
[Urea] ↑
Urea
H2O
Urea
Urea
NaCl
Urea
NaCl
2700
NaCl
2700
2700 mOsm
B

Thick tubule border indicates AQP1-null water impermeable segment of DTL as well as water-impermeable ATL, and TAL. The AQP1- null segment of the DTL is essentially impermeable, to inorganic solutes and water.

Both the ATLs and the DTLs ,(including the AQP1-null segment) are highly permeable to urea. passive NaCl reabsorption without water begins with the prebend segment and is most significant around the loop bend.

Also, Urea moves passively into the entire DTL and early ATL, but this urea-rich fluid further ascends in the ATL, it reaches regions of lower interstitial urea concentration and diffuses out of the ATL again. Thus, the loops act as countercurrent exchangers for urea.

Antidiuretic Hormone:

The renal concentrating ,diluting processes are ultimately and most importantly, dependent on the presence or absence of arginine vasopressin (AVP) ,which is to modulate the water permeability of the collecting duct. AVP, a cyclic hexapeptide ,mol wt 1,099; with a tail of three amino acids, is the antidiuretic hormone (ADH) in humans .

The presence of a basic amino acid ,"arginine or lysine" in the middle of the intact hormone at position 8 ,which is crucial for antidiuresis as is the asparagines at position 5.

AVP which is synthesized in the supraoptic and paraventricular magnocellular nuclei in the hypothalamus. In these nuclei, a biologically inactive macromolecule is cleaved into the smaller, biologically active AVP. Both oxytocin and AVP ,are encoded in human chromosome 20 in close proximity to each other.

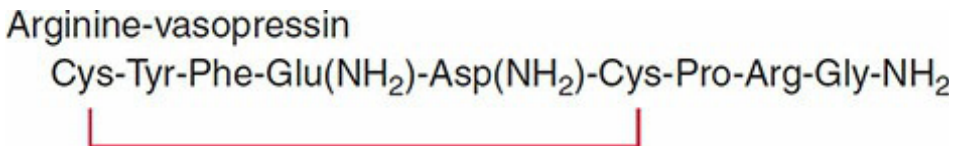
The preprohormonegene is approximately" 2,000 base pairs" in length and comprises three exons . AVP is encoded in the first exon following a signal eptide. Although spanning all three exons, the binding protein Neurophysin which is coded primarily in exon B, and the terminal glycoprotein in exon C. The romoter has cis-acting elements, including a glucocorticoid response element, a cyclic adenosine monophosphate" (cAMP) response element, and four AP-2 binding sites .

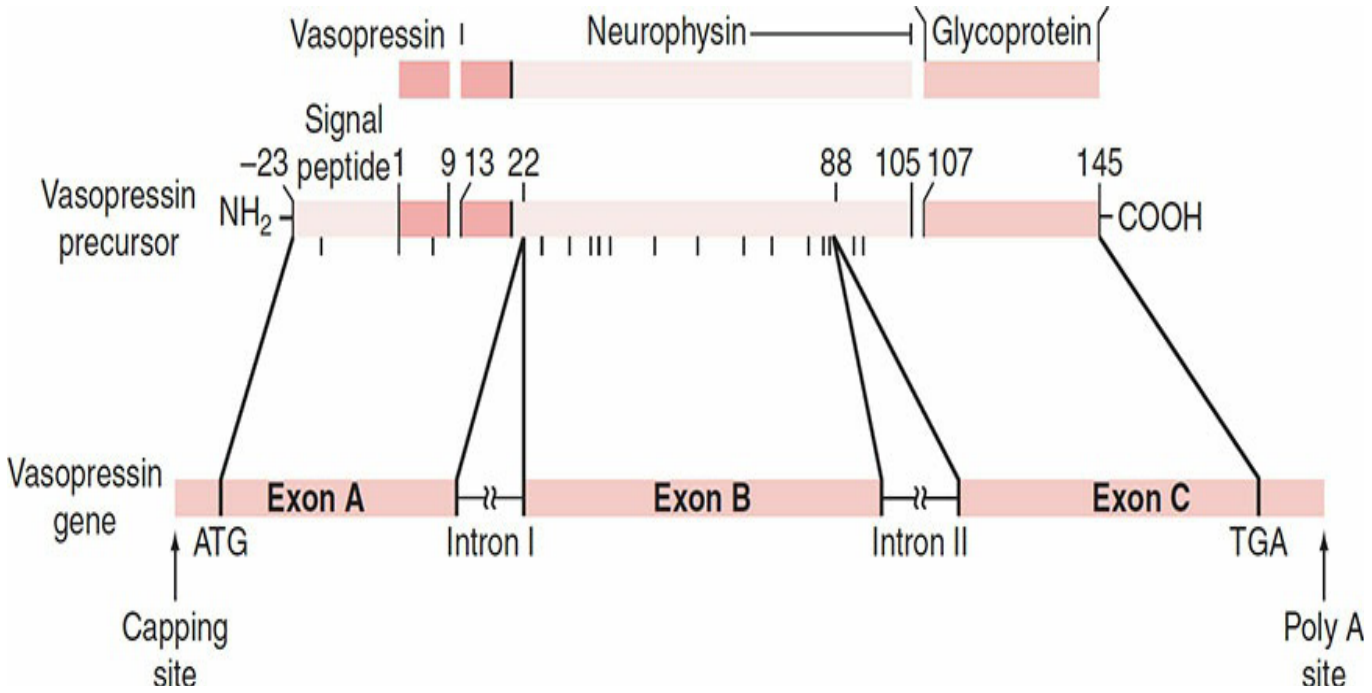
The precursor prohormone, called propressophysin which is cleaved by removal of the signal peptide after translation. Vasopressin, with its binding protein neurophysinII, and the glycoprotein are transported in neurosecretory granules down the axons ,and stored in nerve terminals in the pars nervosa.

There is no known physiologic role of the neurophysins" but they neutralize the negative charge of vasopressin. The release of stored peptide hormone, and its neurophysin into the systemic or hypophyseal portal circulation occurs by an exocytosis.

With increased plasma osmolality, electrical impulses, travel along the axons and depolarize the membrane of the terminal axonal bulbs. The membrane of the secretory granules fuses with the plasma membrane of the axonal bulbs, and then the peptide contents are extruded into the adjacent capillaries.

An autosomal recessive defect that causes AVP deficiency, is afflicted by a single base deletion in exon B. This leads to a shift in the reading frame, with loss of the translational stop code.





The regulation of AVP release from the posterior pituitary is dependent primarily on two mechanisms," osmotic and nonosmotic pathways."

The osmotic regulation of AVP:

It is dependent on osmoreceptor cells in the anterior hypothalamus in proximity but separate from supraoptic nuclei. These cells most likely by altering their cell volume, recognize changes in ECF osmolality.

Cell volume is decreased most readily by substances that are restricted to the ECF, like hypertonic saline ,hypertonic mannitol, and enhance osmotic water movement from cells,these substances are very effective in stimulating AVP release. Since the effects of saline and mannitol are comparable, that the response is due to changes in effective osmolality rather than sodium.

Urea moves readily into cells ,and therefore does not alter cell volume,hypertonic urea does not effectively stimulate AVP release. The effects of increased osmolality on vasopressin release areassociated with measurable ,twofold to fivefold increases in vasopressin precursor messenger RNA (mRNA) in the hypothalamus.

The osmoreceptor cells are very sensitive to changes in ECF osmolality. Increase of ECF osmolality by 1% stimulates AVP release, whereas water ingestion causing a 1% decrease in ECF osmolality suppresses AVP release . A role for members of the transient receptor potential vallinoid family ,TRPV 1 and 4 in osmoregulation has been suggested as knockouts of these proteins . hypernatremic display blunted vasopressin secretion in response to hypertonic stimuli

A close correlation between" AVP and plasma osmolality" has been demonstrated in subjects with various states of hydration. But there are considerable genetically determined individual variations in both the threshold and sensitivity .

In humans, the osmotic threshold for vasopressin release is between "280 and 290 mOsm/kg." The system is so efficient that plasma osmolality usually does not vary more than 1% to 2%, despite great variations in water intake. There is also a close correlation between AVP and urinary osmolality, allowing for the maintenance of tonicity of body fluids.

Nonosmotic Release of Vasopressin:

Vasopressin release can occur in the absence of changes in plasma osmolality ,a number of such nonosmotic stimuli exist, like physical pain, emotional stress, and a decrement in blood pressure or volume are the most prominent ones. A 7% to 10% decrement in either blood pressure or blood volume causes the prompt release of vasopressin.

Because the "integrity of the circulatory volume" takes precedence over mechanisms that maintain tonicity, activation of these nonosmotic pathways overrides any decline in the osmotic stimulus, that otherwise would suppress the hormone's release. This process accounts for the pathogenesis of hyponatremia in various pathophysiologic states, like cirrhosis, heart failure, and several endocrine disorders.

There is considerable evidence for the existence of baroreceptor sensors in the low-pressure venous areas of the circulation, particularly in the atria. Atrial distention causes a decrease in plasma AVP levels, and a water dieresis, this reflex is mediated by the vagus nerve. Alternatively arterial baroreceptors in the aorta and carotid sensors send impulses through the vagus and glossopharyngeal nerves to the nucleus tractus solitarii of the medulla. Unloading of these arterial baroreceptors decreases tonic inhibition and leads to the nonosmotic release of vasopressin.

Denervation of these arterial baroreceptors has been shown to abolish the nonosmotic release of AVP. Angiotensin II is a mediator of AVP release in these states because many of the pathophysiologic states associated with nonosmotic AVP release are characterized by enhanced plasma rennin activity and so increased angiotensin II levels.

"Activation of the sympathetic nervous system," seemed be involved in the nonosmotic stimulation of AVP. The supraoptic nuclei are heavily innervated by noradrenergic neurons. Other pathways that stimulate the nonosmotic secretion of AVP have also been proposed.

The antidiuresis associated with nausea and pain has been ascribed to an emetic and to a cerebral pain center, respectively. A role for baroreceptor pathways has not been excluded even in these settings. Other biogenic amines, "polypeptides", and even cytokines, have been implicated as modulators of AVP release in addition to catecholamines.

SODIUM

Sodium is the major Extra cellular cation in human body.The Cellular homoeostasis and total body sodium content is mainly maintained by body sodium level.Total body water and sodium are major determinant of extra cellular fluid volume and effective arterial blood volume.Imbalance between intake and output of water and serum sodium will lead to sodium abnormalities like hypernatremia and hyponatremia.

Sodium abnormalities like hypernatremia and hyponatremia are the most commonly encountered electrolytes disturbance in hospitalized patients.so that we are commonly doing serum electrolytes in hospitalized patients.Normal serum sodium level is 135 to 145 mmol/lit.If the serum sodium level is less than 135 mmol/lit,it is defined as Hyponatremia.If the serum sodium level is more than 145 mmol/lit ,it is defined as Hypernatremia.

Hyponatremia is most commonly associated with hypotonicity and some times it can be associated with isotonic or hypertonic situation .So that Hyponatremia is subdivided into Hypovolemic hyponatremia,Euvolemic hyponatremia and Hypervolemic hyponatremia,depending on the patients hydration status .

The prevalence of hyponatremia is associated with wide range of disease condition ,pharmacological drug treatment.Hyponatremia may be associated with some risk factors like medical condition ,behavior and characteristics.Mechanism of hyponatremia are Cellular,Hormonal and Neurological processes leads to disturbance in sodium and water balance.

Totally hyponatremia is because of decreased body Sodium or increased total body water or a combination of both. Some medical conditions like Nephrotic syndrome, Cardiac failure and some medications like diuretics, carbamazepine, antipsychotic drugs are associated with alteration in Sodium and water balance. Other risk factors are female sex, advancing age and low body mass.

SODIUM DISORDERS

Serum sodium disorders are because of abnormalities in water homeostasis, leads to changes in the relative ratio of sodium to body water. The vasopressin (Arginine vasopressin) and intake of water playing mainrole in maintenance of serum osmolality.

Any abnormality in these two factors will lead to more cases of hyponatremia and hypernatremia Abnormality in water homeostasis itself leads to hyponatremia and hypernatremia. same manner Abnormalities in sodium itself also leads to hyponatremia and hypernatremia

The release of AVP mainly depend on volume status,.Hypovolemia stimulate the posterior pituitary And release the Arginine vasopressin (AVP),So hypovolemia is associated with higher circulating levels ofArginine vasopressin..Hypervolemia leads to arterial underfilling, , leads to an increase in circulating Arginine vasopressin (AVP) because of neurohumoral activation, leading to water retention and hyponatremia. Sodium concentration will reveal the volume status of a given patient, which will help for diagnostic and therapeutic approach.

HYPONATREMIA

Hyponatremia,defined as a plasma Na+ concentration <135m*M*, more common electrolyte disorder in intensive care unit patients. The prevelance is around 20% in hospitalized patients. Most of the situation t,his disorder is beause of an increase in circulating Arginine vasopressin and/or increased renal sensitivity to Arginine vasopressin. Hyponatremia can also occur due to low solute intake .

The pathophysiology for Inappropriate response Arginine vasopressin (AVP)/SIADH differs in patients with hyponatremia . Depending on Patient clinical and volume status, Hyponatremia is divided into three groups hypovolemic euvolemic and hypervolemic. Most common disorder of electrolytes encountered in clinical practice,occurring in 22% of hospitalizedpatients.

Acute severe hyponatremia can cause substantial morbidity and mortality in intensive care unit patients. Adverse outcomes are higher in hyponatremic patients with wide range of underlying diseases,And overly rapid correction of chronic hyponatremia can cause severe neurological deficits and death.

Hypovolemic Hyponatremia ;

Hypovolemia stimulate the posterior pituitary gland And release the Arginine vasopressin (AVP),So hypovolemia is associated with higher circulating levels of AVP. The increase in circulating Arginine vasopressin (AVP), improving the blood pressure through activation of vascular and baroreceptor V1A receptors and Increases water reabsorption through renal V2 receptors activaton, V2 receptors activation can also lead to hyponatremia in the situation of increased free water intake.

Nonrenal causes of hypovolemic Hyponatremia are Gastro intestinal loss like Diarrhea, tube Drainage and vomiting and insensible loss of sodium ,chloride and water, like sweating and burns in the absence of adequate replacement.

If urine Na+ concentration is <20 m*M*, that patients can be clinically Hypovolemia with extra renal losses like Burns,Pancreatitis,Vomiting Diarrhea Third spacing of fluids ,and Trauma.

If urine Na+ concentration is >20 m*M*, that patients can be clinically Hypovolemia with renal losses like Diuretic excess Osmotic dieresis Salt-losing deficiency Bicarbonaturia with renal tubal acidosis and metabolic alkalosis Cerebral salt wasting syndrome Mineral corticoid deficiency Ketonuria.

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The Renal causes of hypovolemic hyponatremia share an inappropriate loss of sodium and chloride in the urine, leads to volume loss and Higher level of arginine vasopressin level .So in this situation urine sodium concentration is >20 m*M*..

In primary adrenal insufficiency and other situation of hypoaldosteronism ,there will be deficiency in aldosterone or its renal effects can lead to hyponatremia hyperkalemia and hypotension, with high urine Na+ concentration greater than 20 m*M* .

Thiazide diuretics produce hyponatremia through a number of mechanisms They are Mainly thiazides do not inhibit the renal concentrating mechanism, so that circulating Arginine vasopressin retains a full effect on renal water retention.and others are diuretic-induced volume depletion and increased water intake.

Loop diuretics inhibit sodium chloride and potassium absorption in the Thick ascending loop of henle,so it blunts the countercurrent mechanismand reduces the urine concentration ability .So Loop diuretics are not frequently associated with hyponatremia.

Salt-losing nephropathie like, Medullary cystic disease, Reflux nephropathy , Interstitial Nephropathy ,Acute tubular necrosis and postobstructive uropathy can lead to hyponatremia when intake of sodium is poor.,because of renal tubular function impairment.

The cerebral salt wasting syndrome will have hypovolemia, hyponatremia with Inappropriate natriuresis .More often it is associated with intracranial disease like Meningitis , Encephalitis, Subarachnoid hemorrhage, Craniotomy, and, Traumatic brain injury. Differentiation from the SIADH critical because cerebral salt wasting syndrome will respond to sodium chloride – replacement .

Glycosuria, ketonuria in diabetic acidosis/ alcoholic ketoacidosis/in starvation and bicarbonaturia in metabolic alkalosis and in renal tubular acidosis where Increased excretion of an osmotically active poorly reabsorbable and nonreabsorbable solute may produce volume depletion and hyponatremia.

Hypervolemic Hyponatremia ;

In hypervolemic hyponatremia There is an increase in total-body sodium,chloride which is accompanied with proportionately greater increase in total-body water, leads to reduced serum sodium concentration.

The pathophysiology Of hypervolemic hyponatremia in the sodium-avid edematous disorders like Nephrotic syndrome, Cirrhosis and Congestive heart failure similar hypovolemic hyponatremia and arterial underfilling and decreased circulatory integrity is because of particular cause like cirrhosis with peripheral vasodilation ,cardiac dysfunction in Congestive heart failure (CHF).

If urine sodium more than 20,it may be acute or chronic renal failure. If urine sodium less than 20,it may be Nephrotic syndrome, Cirrhosis and Congestive heart failure Urine sodium concentration , very low even after hydration with normal saline. this sodium -avid state can be improved by diuretic therapy.

The degree of hyponatremia gives a indirect index of the associated neurohumoral activation and It is an very important prognostic indicator in hypervolemic hyponatremia.

Euvolemic Hyponatremia

Euvolemic hyponatremia mainly due to expansion of total body water because of excessive intake of water in the state of an impaired urinary dilution. The defective urinary dilution is often caused by a defect in the osmotic suppression of AVP The first One , A nonhemodynamic stimulus like nausea ,cortisol deficiency.The other one , primary defect in osmoregulation produced by disorders like pneumonia , malignancy, and stroke.

Moderate to severe hypothyroidism Patients may develop Euvolemic hyponatremia even after achieving aeuthyroid state. Secondary adrenal insufficiency due to pituitary disease can produce Severe hyponatremia .

The glucocorticoiddeficiency in the secondary adrenal failure is associated with euvolemic hyponatremia. Glucocorticoids have a negative feedback on Arginine vasopressin release by the posterior pituitary so that hydrocortisone replacement in these patients will normalize the Arginine vasopressin (AVP) response to osmolality. But Aldosterone deficiency in primary adrenal insufficiency causes hypovolemic hyponatremia.

The syndrome of inappropriate antidiuresis (SIAD) is the most frequent cause of euvolemic hyponatremia. It can have many causes .They are Ectopic production of AVP by GIT Cancers ,lung cancer and other neoplasms Eutopic release induced by various drugs Like SSRIs,and various disease like Pneumonia. Exogenous administration of Arginine vasopressin and large doses of oxytocin.

The ectopic forms because of abnormal expression of the AVP-NPII gene, caused by primary and metastatic malignancies. The eutopic forms mostly associated with strokes ,Acute infections and manyother neurologic injuries,diseases

The mechanisms by which these diseases interfere with osmotic suppression of Arginine vasopressin is not known The defective osmoregulation may take any of four distinct forms Reset osmostat is one of the most common form ,Here Arginine vasopressin secretion fully responsive to changes in plasma osmolarity and sodium, but the set point of the osmoregulatory system is abnormally low.

They can able to suppress plasma AVP and dilute their urine if their fluid intake is high enough to reduce their plasma sodium and osmolarity to the new set point some patients have inappropriate antidiuresis ,but no demonstrable defect in the osmoregulation of plasma Arginine vasopressin.

Some patients , (young boys) the inappropriate antidiuresis has been detected,this is because of activating mutation of the V2 receptor gene. This rare l variant may be classified as familial nephrogenic SIAD ,NSIAD

.

Patients with SIADH , not euvolemic .They are subclinically volume-expanded, because of AVP induced sodium chloride and water retention Serum uric acid is low,less than 4mg/dL in SIADH Patients, because of suppressed proximaltubular transport in the setting of increased distal tubular sodium,chloride and water transport.

But patients with hypovolemic hyponatremia will be hyperuricemic, because of shared activation of proximaltubular Na+-Cl– and urate transport.Common causes of SIADH are central nervous system Diseases like tumor, subarachnoid hemorrhage, meningitis.and pulmonary disease like tuberculosis, pneumonia,And pleural effusion.

SIADH can occurs with malignancies, mostly with small-cell lung carcinoma ,75% of malignancy associated with SIADH. 10% of this patients will have a plasma sodium concentration <130 m*M* at Presentation SIADH also a frequent complication of certain drugs Like Tricyclic Antidepressants (TCA), the selective serotonin reuptake inhibitors (SSRIs). Other drugs can produce the renal effect of Arginine vasopressin, but no direct effects on circulating AVP levels .

Criteria for Diagnosing SIADH

- ✓ Decreased effective osmolality of the extracellular fluid.
- ✓ Inappropriate urinary concentration (Uosm >100 mOsmol/kg H2O) with normal renal function) at some level of plasma hypoosmolality.
- ✓ Clinical euvolemia.
- ✓ Elevated urinary sodium excretion (>20 mmol/L) while on normal salt and water intake.
- ✓ Absence of other potential causes of euvolemic hypo-osmolality
- ✓ Normal renal function and absence of diuretic use, particularly thiazide diuretics.

Others are

-Low blood urea nitrogen (BUN),less than 10 mg/dl;

-Hypourecemia less than 4 mg/dl;

CAUSES OF THE SYNDROME OF INAPPROPRIATE ANTIDIURESIS (SIAD)

Malignant Diseases	Pulmonary Disorders
Carcinoma	Infections
Lung	Bacterial pneumonia
Small cell	Viral pneumonia
Mesothelioma	Pulmonary abscess
Oropharynx	Tuberculosis
Gastrointestinal tract	Aspergillosis
Stomach	Asthma
Duodenum	Cystic fibrosis
Pancreas	Respiratory failure associated with positive-pressure breathing
Genitourinary tract	
Ureter	
Bladder	
Prostate	
Endometrium	
Endocrine thymoma	
Lymphomas	
Sarcomas	
Ewing's sarcoma	

CAUSES OF THE SYNDROME OF INAPPROPRIATE ANTIDIURESIS (SIAD)

Drugs	Other Causes
Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Chlorpropamide	Idiopathic
SSRIs	Transient
Tricyclic antidepressants	Endurance exercise
Clofibrate	General anesthesia
Carbamazepine	Nausea
Vincristine	Pain
Nicotine	Stress
Narcotics	
Antipsychotic drugs	
Ifosfamide	
Cyclophosphamide	
Nonsteroidal anti-inflammatory drugs	
MDMA ("ecstasy")	
AVP analogues	
Desmopressin	
Oxytocin	
Vasopressin	

Low Solute Intake and Hyponatremia

Hyponatremia can occur in patients with very low intake of dietary solutes. Mostly It happens in alcoholics whose only nutrient is beer, so it is referred as beer potomania.

Beer having very low salt and very low protein content. This is also occur in nonalcoholic patients with restricted solute intake due to nutrient restricted diets,like extreme vegetarian diets.

This Patients classically present with hyponatremia and very low urine osmolality ,<100–200 mOsm/kg,with urine sodium concentration is<10–20 m*M*.

The basic abnormalityis the inadequate dietary intake of solutes and the decreased urinary solute excretion which limits water excretion . AVP levels is not been reported with beer potomania patients , but they can be suppressed / rapidly suppressible with saline replacement.

A normal diet and saline hydration Can correct the causative deficit in urinary solute excretion, so that beer potomania patients classically correct their plasma sodium concentration .

Clinical Features of Hyponatremia

Hyponatremia , water movement down the osmotic gradient from the hypotonic ECF to the ICF will produces generalized cellular swelling. The symptoms of hyponatremia,primarily neurologic,because of the development ofcerebral edema within a rigid skull.

The CNS response to acutehyponatremia , an increase in interstitial pressure,leads to shunting of Extra cellular fluid and solutes from the interstitial space intothe cerebrospinal fluid and then into the systemic circulation,which is accompanied by efflux of the major intracellular ions sodium, potassium and Chloride from brain cells.

- Acute hyponatremia – < 48 hours
- Chronic hyponatremia - > 48 hours

Mild hyponatremia (130-134)

Asymptomatic or subtle changes in physical and mental function

Moderate hyponatremia (120-129)

Nausea,Vomiting,Headache,Malaise,Drowsiness and Lethargy

Severe hyponatremia (<120)

Seizure,Coma,and Death

This manifestation can be influenced by the speed of onset of hyponatremia.

Acute hyponatremic encephalopathy occurs when these volumeregulatory mechanisms are overwhelmed by a rapid decrease in tonicity,results in acute cerebral edema. Initial symptoms are nausea, headache, vomiting. Some time patients can develop seriouscomplications like seizure activity, brainstem herniation, coma,and death.

Main complication of acute hyponatremia ,normocapneic and hypercapneic respiratory failure.The hypoxia due to respiratory failure canamplify the neurologic injury. In this situation ,Normocapneic respiratory failure isclassically due to noncardiogenic, that is neurogenicpulmonary edema, with normal pulmonary capillary wedge pressure.

Acute symptomatic hyponatremia , a medical emergency, occus in a number of particular settings .

Causes of Acute Hyponatrem ia

-Iatrogenic,
-premenopausal women,
-Polydipsia,
-Postoperative,
- Colonoscopy preparation
-uterine surgery,
-During -TURP
-Exercise
-Recent institution of thiazides,
-MDMA ,ecstasy,Molly ingestion,
- Multifactorial.

Women, before menopause more likely to develop encephalopathy ,severe neurologic sequelae than man. Acute hyponatremia may develop as an iatrogenic likewhen hypotonic intravenous fluids given to postoperative patients with an increase in circulating arginine vasopressin

Exercise associated hyponatremia, an important problem for marathons and other eventswhich has been linked to both excessive free water intake and nonosmotic increase in circulating arginine vasopressin.

The drugs like Molly and ecstasywhich have anactive ingredient of MDMA, 3,4-methylenedioxymethamphetamine, Produce a rapid and potent induction of both thirst and arginine vasopressin leads to severe acute hyponatremia.

Persistent, chronic hyponatremia results from an efflux of organic osmolytes from brain cellslike taurine,creatine, betaine, glutamate, and myoinositol. This reduces the intracellular osmolality , the osmotic gradient and leads to water entry. This reduction in intracellular osmolytes will take 48 hour.This time duration that clinically defines chronic hyponatremia.

This time durationis more important for the treatment of hyponatremia . This cellular response in chronic hyponatremia does not fully protect the patients from hyponatremia symptoms like vomiting, nausea, seizures,and confusion.

If plasma sodium concentration <125 Mm,these symptoms will be often seen.Some time patients may be asymptomatic,but they have subtle gait and cognitive defects .Chronic symptomatic hyponatremia increases the risk of falls,So correction of hyponatremia will reverse the gait defect and cognitive defect.

Chronic hyponatremia also increases the risk of bony fractures because of hyponatremiaassociated reduction in bone density and associated neurological dysfunction.So,correction of the plasma Na+ concentration in patients with chronic hyponatremia is very important ,even in the absence of clinical symptoms.

The asymmetry of the cellular response to correction of plasma Na+ concentration will complicate the chronic hyponatremia treatment.Particularly, the reaccumulation of organic osmolytes by brain cells has been attenuated and delayed ,because osmolality increases after correction of hyponatremia.Sometimes it leads to degenerative loss of oligodendrocytes and an osmotic demyelination syndrome (ODS).

Rapid correction of hyponatremia more 8 to10 m*M* in 24 hours and 18 m*M* in 48 hours, associated with a disruption in integrity of the blood-brain barrier and allows the entry of immune mediators which are responsible for demyelination. The lesions of osmotic demyelination syndrome Particularly affect the pons, where the delay in the reaccumulation of osmotic osmolytes has been pronounced.

Patients with central pontine myelinolysis may present with symptomaticaly one or more days after overcorrection of hyponatremia.It can present as quadriparesis,paraparesis ,diplopia,dysphagia, dysarthria, a lockedin syndrome, and loss of consciousness.

Other areas of the brain may be involved in osmotic demyelination syndrome.Most commonly associated with pons lesion ,and also the lesions of extrapontine myelinolysis can occur in the cerebellum, lateral geniculate body, thalamus, putamen, cerebral cortex and subcortex.

So Clinical presentation of Osmotic demyelination syndrome may vary according to the extent and localization of extrapontine myelinolysiswith the development of mutism,ataxia, parkinsonism, catatonia and dystonia.

Relowering of plasma sodium concentration after rapid correction of hyponatremia may prevent or attenuatethe osmotic demyelination syndrome. Some times, appropriately slow correction of sodium may be associated with Osmotic demyelination syndrome.

Patients with risk factors like malnutrition, hypokalemia, alcoholism and liver transplantation are more susceptible to this one.So during correction of hyponatremia ,appropriately slow connection of sodium and clinical monitoring is very important. Because early recognition and early intervention will prevent or attenuate the severe complications.

DIAGNOSTIC EVALUATION OF HYPONATREMIA

Clinical assessment of the hyponatremic patients mainly focus on the underlying etiology .So detailed clinical history and detailed drug history is very important.A careful clinical assessment of the patient's volume status is mandatory for the classical diagnostic approach to hyponatremia .

Most of the time Hyponatremia is multifactorial, particularly when severe clinical manifestations are present.So clinical evaluation should focus on allthe possible causes for excessive circulating arginine vasopressin like drugs,volume status, and presence of nausea or pain.

STEP 1 :Serum Osmolality

Serum Osmolality,(mosm/kg)

=(2 x Na+) + (glucose/18) + (BUN/2.8)

- Hypertonic – (>295)
  - Hyperglycemia, Mannitol, Glycerol
- Isotonic – (280-295)
  - Pseudo-hyponatremia from elevated lipids or protein
- Hypotonic – (<280)
  - Excess fluid intake, Low solute intake, Renal disease, SIADH,Hypothyroidism, Adrenal insufficiency, CHF, Cirrhosis, etc.

STEP 2 :Volume Status

Second Assess volume status (extracellular fluid volume)

Hypotonic hyponatremia has 3 main Etiologies,

- ❖ Hypovolemic – both water and Na decreased (H20 < Na)
    - Diarrhea, Vomiting,Dehydration, Malnutrition, etc

- ❖ Euvolemic – water increased and Na stable
    - SIADH, Thyroid disease, Primary polydipsia

- ❖ Hypervolemic – Both water increased , Na increased (H2O > Na)
    - CHF, cirrhosis, renal failure

STEP 3 :Urine Studies

For Euvolemic hyponatremia, check urine osmolality,

- ❖ Urine osmolality <100 - Excess water intake
    - o Primary polydipsia, Tap water enemas, Post TURP

- ❖ Urine osmolality >100 - Impaired renal concentration
    - o SIADH, Hypothyroidism, Cortisol deficiency

Check urine sodium & calculate FeNa %

- ✓ Low urine sodium (<20) and low FeNa (<1%) implies the kidneys are appropriately reabsorbing sodium
- ✓ High urine sodium (>20) and high FeNa (>1%) implies the kidneys are not functioning properly.

Radiological imaging may be needed to see whether patients have a Central nervous system or pulmonary cause for hyponatremia. Some time chest x-ray may be normal. Small cell carcinoma of the lung may be missed on routine chest x ray.So CT throax should be considered in patients with high risk for this tumor ,example patients with a smoking history.

Laboratory investigation should do serum osmolality to exclude pseudohyponatremia.Pseudohyponatremia, the coexistence of hyponatremia with a normal /increased plasma tonicity.

Most of the clinical laboratories will measure plasma sodium concentration by testing diluted samples with automated ionsensitive electrodes.For correcting this dilution , assume that plasma is 93% water. Because of extreme hyperlipidemia or hyperproteinemia,this correction factor may be inaccurate in patients with pseudohyponatremia.

Serum lipid and protein makes up a greater percentage of plasma volume. The measured osmolality should be converted to the effective osmolality that is tonicity by subtracting the measured concentration of urea .HyponatremiaPatients usually have an effective osmolality of less than 275 mOsm/kg.

Elevated creatinine and BUN in routine investigationsindicates renal dysfunction which is a important cause of hyponatremia. Hyperkalemia can suggest adrenal insufficiency ,hypoaldosteronism.

Serum glucose should be measured. For every 100mg/dL increase in glucose,there will be plasma sodium concentration falls 1.6 to 2.4 mM due to glucoseinduced water efflux from cells.This true hyponatremia will resolve after correction of hyperglycemia. Measurement of serum uric acid should also be performedPatients with SIADH will be hypouricemic ,volume depleted patients will be hyperuricemic,so Serum uric acid should be measured.

Adrenal, pituitary and thyroid function can also be tested.Because Hypothyroidism ,Secondary adrenal failure due to pituitary insufficiency are important causes of Euvolemic hyponatremia. In primary adrenal failure causes hypovolemic hyponatremia. Cosyntropin stimulation test is important to assess the primary adrenal insufficiency.

Urine osmolality and urine electrolytes are important tests for the initial evaluation of hyponatremia.In Hypovolemic hyponatremia,urine Na^+ concentration is less than 20–30 mM. And hypervolemic, sodium avid syndrome like CHF will also have same values.But patients with SIADH will excrete urine sodium concentration that is more than 30 m*M*. There is substantial overlap in urine sodium concentration values in patients with hypovolemic hyponatremia and SIADH.

The Gold standardfor the Diagnosis of hypovolemic hyponatremia ,the plasma sodium concentration will be corrected after normal saline hydration. Patients with thiazide associated hyponatremia can present with higher urine sodium concentration than expected urine sodium concentration. and other findings suggest SIADH

Diagnosis of SIADH in these patients will defer until 1 to 2 weeks after discontinuing the thiazide.

A urine osmolality less than 100 mOsm/kg , suggestive of polydipsia.Urine osmolality morethan400 mOsm/kg suggestive of excess AVP .Intermediate values are suggestive of multifactorial pathophysiology ,like AVP excess with significant component of polydipsia.

Beer potomania Patients ,hyponatremia due to decreased solute intake have urine Sodium concentration less than 20 mM.*U*rine osmolality will be in the range of less than 100 to the low 200.The urine potassium concentration is required to calculate the urine to plasma electrolyte ratio that is useful to predict the response to fluid restriction .

HYPONATREMIA TREATMENT

There are three major considerations which will be guide the therapy of hyponatremia.

- The presence and severity of symptoms suggest the urgency and goals of therapy.Patients with acute hyponatremia can present with symptoms ranges from nausea, vomiting, headache,seizures, obtundation, and central herniation.patients with chronic hyponatremia that is present for more than 48 hours,less likely to have severe symptoms.

- Chronic hyponatremia patients are very high risk for developing osmotic demyelination syndrome if plasma sodium concentration is corrected More than 8 to 10 mM within the first 24 hours and more than 18 mM within the first 48 hours.

- The response to interventions like Isotonic saline, hypertonic saline,AVP antagonists may be highly unpredictable.So during corrective therapy, frequent monitoring of plasma sodium concentration is very essential.

When considering the treatment of patients with hyponatremia;
Five issues must be addressed

- ✓ Estimation of the sodium deficit if sodium is to be given
- ✓ Optimal method of raising the plasma sodium concentration
- ✓ Risk of osmotic demyelination
- ✓ Appropriate rate of correction to minimize this risk
- ✓ Management of the patient in whom overly rapid correction has occurred

- Once the plasma sodium concentration has been established; then appropriate therapy should be instituted.The focus should be on treatment of the underlying cause withdrawal of the underlying cause.

- Patients with euvolemic hyponatremia due tohypothyroidism,SIADH, and secondary adrenal failure will respond to successful treatment of the underlying cause,with an increase in plasma Na+ concentration, Pharmacologic therapy to increase the plasma sodium concentration is needed in some of the SIADH case .Because all causes of SIADH ara not reversible.

- Hypovolemic hyponatremia is usualy respond to intravenous hydration with isotonic normal saline.So it causes rapid reduction in circulating AVP and a brisk water diuresis.If the history suggests that hyponatremia has been chronic (present for more than 48 hours),we have to reduce the rate of correction.

- Hypervolemic hyponatremia because ofcongestive heart failure is usually respond to improved therapy of the underlying cardiac pathology ,Example After the institution or intensification of angiotensin converting enzyme inhibition.

- Patients with hyponatremia because of beer potomania , low solute intake is usually respond rapidly to intravenous saline and the resumption of a normal diet.Patients with beer potomania whom are very high risk for developing Osmotic demyelination syndrome, because the associated alcoholism, malnutrition,hypokalemia, and high risk of overcorrecting the plasma sodium concentration.

- Water deprivation is a cornerstone of the therapy of chronic hyponatremia (present more than 48 hours). patients are excreting minimal electrolytefree water should require strict fluid restriction. It is very difficult for patients with SIADH .Because their thirst has been also inappropriately stimulated.

- The urine to plasma electrolyte ratio (urinary [Na+] + [K+] divided by plasma [Na+]) can be exploited as a quick indicator of electrolyte free water excretion .Patients with a ratio of more than 1 must be aggressively restricted less than 500 mL/day. Patients with a ratio of ~1 must be restricted to 500 to 700 mL/day.Patients with a ratio less than 1 must be restricted to <1 L/day.

- Potassium replacement will serve to increase plasma Na+ concentration In hypokalemic patients.The plasma sodium concentration is a functional of both exchangeable sodium and exchangeable potassium divided by total body water. Aggressive correction of potassium have the potential to over correct the plasma sodium concentration even in the absence of hypertonic saline.

- Plasma sodium concentration can also tend to respond to an increase in dietary solute intake. The dietry solute increases the ability to excrete free water. Oral urea or salt tablets for this purpose is usually not practical. Oral urea or salt tablets is also not well tolerated.

- Pharmacologic therapy to increase their plasma Na+ concentration is needed when therapy with fluid restriction, potassium replacement and increased solute intake fails to improve plasma sodium concentration Patients with SIADH have respond to combined therapy with oral furosemide 20 mg twice a day .

- Higher doses may be needed in renal Insufficiency and oral salt tablets. Furosemide serves to inhibit the renal countercurrent mechanism; blunt urinary concentrating ability.The salt tablets counteract diuretic associated natriuresis.

- Patients whose sodium levels do not increase in response to furosemide and salt tablets,in this situation Demeclocycline can be used..Demeclocycline, a potent inhibitor of principal cells, this agent can be associated with a reduction in GFR, because of direct renal toxicity and excessive natriuresis Demeclocycline should be avoided in cirrhotic patients, who are at higher risk of nephrotoxicity due to drug accumulation.

- Vaptans ,AVP antagonists are highly effective in SIADH patients and in hypervolemic hyponatremia patients like heart failure , cirrhosis where Vaptans increasing the plasma sodium concentration due to their aquaretic effects that is augmentation of free water clearance. Most of these agents particularly antagonize the V2 AVP receptor. Now Tolvaptan is the only oral V2 antagonist , approved by the U.S. Food and Drug

- Administration. Conivaptan, the only intravenous vaptan which is a mixed V1A/V2 antagonist. The side effect is risk of hypotension due to V1A receptor inhibition. Vaptans therapy must be started in a clinical setting with a liberalization of fluid restriction more than 2 L/day.During Vaptans therapy ,close monitoring of plasma Na+ concentration is must.

- Vaptans are approved for the management of all hyponatremic patients ,but hypovolemic hyponatremia and acute hyponatremia, where vaptans usage are not completely clear. Oral tolvaptan is the most appropriate drug for the

management of significant and persistent SIADH like in small-cell lung carcinoma,lung infection and CNS disease which are not responded to water restriction or oral furosemide and salt tablets.

- Chronic tolvaptan therapy may be lead to abnormalities in liver function tests, So the use of this agent must be restricted to less than 1 to 2 months. Treatment of acute symptomatic hyponatremia is hypertonic 3% saline ,513 mM to acutely increase plasma sodium concentration by 1 to 2 m*M* per hour to a total of 4 to 6 mM.
- This modest increase in plasma sodium concentration is sufficient to solve the severe acute symptoms, after that corrective guidelines for chronic hyponatremia is appropriate .

- Many equations have been developed to estimate the required rate of hypertonic saline, which has an sodium chloride concentration of 513 m*M*. The traditional approach , to calculate an sodium Deficit where the sodium deficit = 0.6 × body weight × (target plasmaSodium concentration – starting plasma sodium concentration) followed by a calculation of the required rate.

- Even though so many methods usedto determine the rate of sodium administration, the increase in plasma Na+concentration may be highly unpredictable during treatment with hypertonic saline, because of rapid changes in the underlying physiology.

- Plasma sodium concentration must be monitored every 2 to 4 hours,during treatment, with appropriate changes in therapy based on the observed rate of change.

- The patients with acute pulmonary edema or hypercapneic respiratory failure in acute hyponatremia, supplemental oxygen and ventilatory support is also needed. I.V loop diuretics can treat acute pulmonary edema .

- I.V loop diuretics can also increase free water excretion by interfering with the renal countercurrent multiplication system. Vaptans,AVP antagonists do not have an approval for the managementof acute hyponatremia.

- In chronic hyponatremia ,to avoid osmotic demyelination syndrome ,The rate of plasma sodium correction must be comparatively slow , less than 8 to 10 mM in the first 24 h and less than 18 mM in the first 48 Hours . Patients with particular risk for osmotic demyelination syndrome such as alcoholics or hypokalemic patients, lower target rates are appropriate.

- Overcorrection of the plasma sodium concentration may occur when Arginine vasopressin levels rapidly normalize, like following glucocorticoid replacement of patients with hypopituitarism ,secondary adrenal failure and following the treatment of patients with chronic hypovolemic hyponatremia with intravenous saline .

- Around 10% of patients treated with vaptans will overcorrect.If water intake is not liberalized, the over correction risk will be increased. In the event that the Overcorrection of plasma sodium concentration following therapy with hypertonic saline, isotonic saline, or vaptans may occur.

- This hyponatremia will be safely reinduced and stabilized by the administration of the desmopressin acetate (DDAVP),AVP agonist and the administration of free water, specifically intravenous 5% Dextrose water.The aim will be to prevent and reverse the development of osmotic demyelination syndrome.

- The treatment of patients with severe hyponatremia may be initiated with the twice daily administration of DDAVP (desmopressinacetate) to maintain constant AVP bioactivity. Hypertonic saline can be combined with this,for slowly correcting the serum sodium in a more controlled fashion.So that It reduces the upcoming risk of overcorrection.

GENERAL PRINCIPLES OF TREATMENT

Primarily determined by the severity of symptoms and cause of the hyponatremia.

1. Symptomatic hyponatremia (seizures, or coma)

Likely to occur with an acute case and marked reduction in the plasma sodium concentration, Aggressive therapy is required.

2. Chronic but significant hyponatremia

Less severe neurologic symptoms occur fatigue, nausea, dizziness, gait disturbances,confusion, lethargy, and muscle cramps.

These symptoms typically do not mandate aggressive therapy.

Water restriction

Primary therapy for hyponatremia in edematous states like SIADH, primary polydipsia, and advanced renal failure.

Sodium chloride administration

Usually as isotonic saline or increased dietary salt given to the patients with true volume depletion, adrenal insufficiency, and in some cases of SIADH.

- Contraindicated in edematous patients (heart failure, cirrhosis, renal failure) since it will lead to exacerbation of the edema Hypertonic saline, generally recommended only for patients with symptomatic or severe hyponatremia.

- The increase in plasma Na+ concentration can be highly unpredictable during treatment with hypertonic saline due to rapid changes in the underlying physiology.

- Patient should be monitored carefully for changes in neurologic and pulmonary status, and serum electrolytes.It should be checked frequently every 2 - 4 hours.

Goal:

- Urgent correction by 1-2 mmol/h upto 4-6 mmol/L, to prevent brain herniation and neurological damage from cerebral ischemia.

- Upper limit for correction 10-12 mmol/L in any 24hour period,18 mmol/L in any 48-hour period.

- Minimum correction of serum [Na] by 4-8 mmol/L per day, with a lower goal of 4-6 mmol/L per day if the risk of ODS is high.

Limits not to exceed;

8-10 mmol/L in any 24-hour period.

Treatment of hypovolemic hyponatremia

Diuretic related;

Discontinuation of thiazides and correction of volume deficits.

Mineralocorticoid deficiency-

Volume repletion with isotonic saline, Fludrocortisone for mineralocorticoid replacement

- All other renal causes of hypovolemic hyponatremia will rapidly responds to intravenous hydration with isotonic normal saline and a rapid reduction in circulating AVP.And concurrently treat the underlying cause also.

-Extra renal causes of hypovolemic hyponatremia,Treat the underlying etiology and it also rapidly responds to intravenous hydration with isotonic normal saline and a rapid reduction in circulating AVP.

Treatment of euvolemic hyponatremia

- SIADH ;

For most cases of mild to moderate SIADH, Fluid restriction represents the cheapest and least toxic therapy. (fluid restriction 500 mL/d below the 24-hour urine volume.

Failure to water restriction;

- Vaptans
- Democlocycline 150- 300 mg PO tid or qid -Fludrocortisone 0.05-0.2 mg bids

- -Glucocorticoid deficiency;
    - Glucocorticoid replacement at either maintenance or stress doses, depending on the degree of intercurrent illness.

- -Severe Hypothyroidism;
    - Thyroid hormone replacement; several days may be needed to normalize the serum Na.

- -Drugs,
    - Stop that drug and go to alternate drug

- -Pain/Stress,

Good analgesic and good anxiolytic drugs to reduce the pain and anxiety.

Treatment of hypervolemic hyponatremia,

Heart Failure;

Patients with mild to moderate symptoms, begin with fluid restriction (1 L/d total) and, if signs of volume overload are present, administer loop diuretics. If the serum sodium does not correct to the desired level, lift the fluid restriction and start either conivaptan or tolvaptan.

Cirrhosis;

Severe daily fluid restriction, Vaptans an alternative choice if fluid restriction has failed to maintain a serum Na,130 mmol/L; tolvaptan use should be restricted to cases where the potential clinical benefit outweighs the risk of worsened liver function, such as in patients with end stage liver disease and severe hyponatremia who are awaiting imminent liver transplantation.

CKD;

Restricting fluid intake. Aquaretics, vaptans can be employed{not be expected to cause a clinically significant aquaresis with severe renal impairment (ie, serum creatinine >2.5 mg/dL)}.

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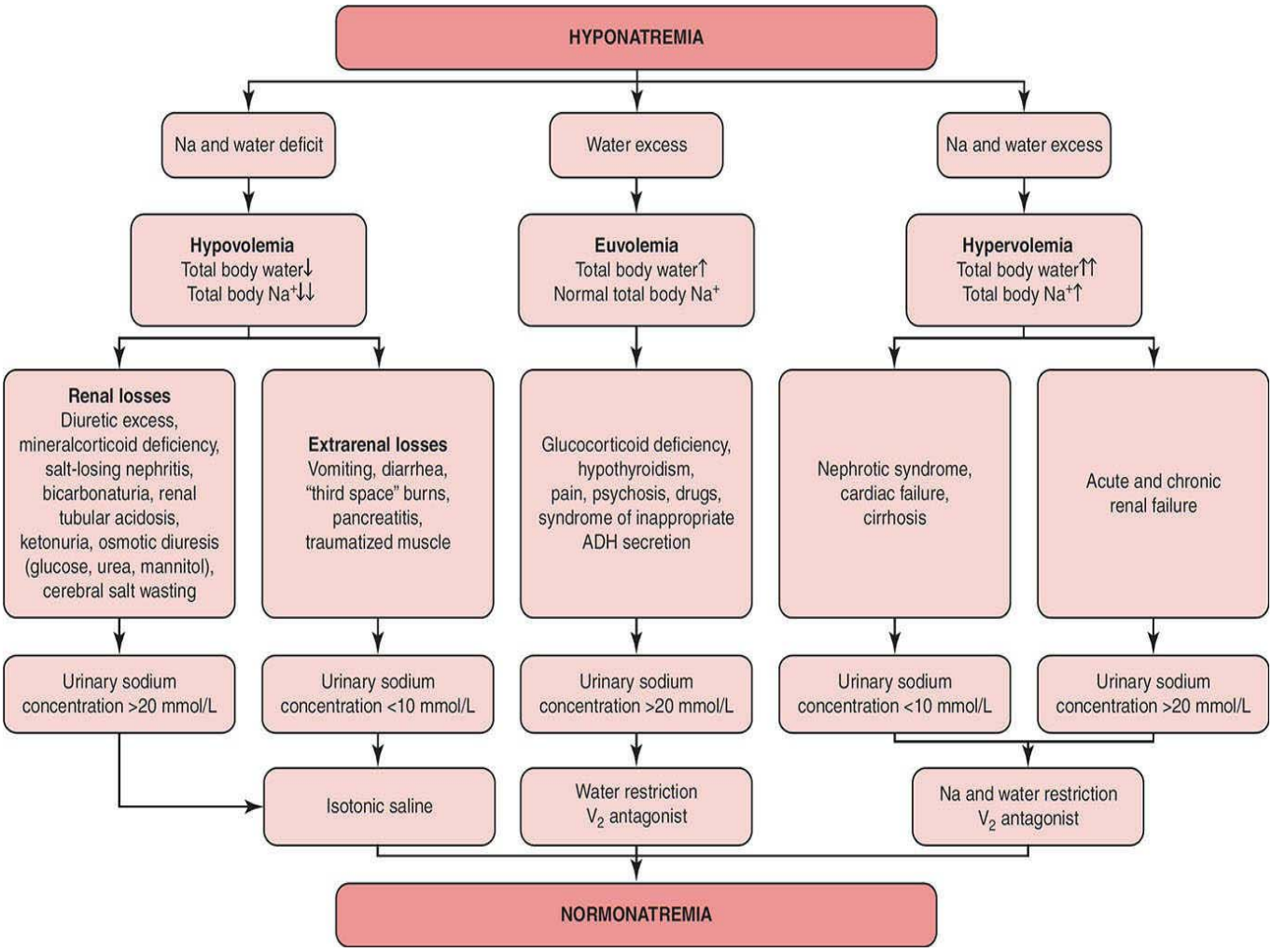
Diagnostic and therapeutic approach to the hyponatremic patient



MATERIALS AND METHODS

SETTING :

The study will be conducted on 200 Icu patients , admitted at Government Rajaji Hospital & Madurai Medical College during the study period

patients with Normal sodium levels (135-145) are taken as controls

DESIGN OF STUDY :

Prospective study

PERIOD OF STUDY :

6 Months

Inclusion criteria :

- All Icu patients who are having euvolemic hyponatremia
- Age > 15 yrs & < 60 yrs
- Serum sodium less than 135

Exclusion criteria

- Age <15 yrs & > 60 yrs
- CKD
- CAD
- Hyperglycemia
- Hyperlipidemia
- Hyperproteinemia
- Pregnancy

LABORATORY INVESTIGATIONS

- Serum Sodium, S. Potassium
- CBC
- Blood sugar
- RFT
- Serum Osmolality
- Serum uric acid
- Urine Routine Examination
- Urine Osmolality
- Urine Sodium, Urine Potassium
- CXR,CT-Chest,CT-brain if needed
- Thyroid function tests, Serum Cortisol if needed

ANTICIPATED OUTCOME

Hyponatremia as an independent prognostic factor for predicting the morbidity and mortality of Icu patients who are having euvolemic hyponatremia.

Early recognisation and appropriate management of hyponatremia will improve the outcome

STUDY PROTOCOL

Clinical assessment of the hyponatremic patients mainly focus on the underlying etiology .So detailed clinical history and detailed drug history is very important.A careful clinical assessment of the patient's volume status is mandatory for the classical diagnostic approach to hyponatremia.

Most of the time Hyponatremia is multifactorial, particularly when severe clinical manifestations are present.So clinical evaluation should focus on allthe possible causes for excessive circulating arginine vasopressin like drugs,volume status, and presence of nausea or pain

DESIGN OF STUDY;

Prospective analytical study

PERIOD OF STUDY;

March 2018 to August 2018

COLLABORATING DEPARTMENTS;

Department of Medicine, and ICU, Department of Biochemistry.

CONFLICT OF INTEREST- Nil

CONSENT- Individual written and informed consent.

FINANCIAL SUPPORT- Nil

ANALYSIS - Statistical analysis

PARTICIPANTS*:* 200 ICU Patients with Euvolemic hypontremia , Govt. Rajaji Hospital, Madurai.

Method of study

This study was conducted in Govt. Rajaji Hospital, Madurai which is affiliated to Madurai Medical College. This study subjects were selected from the patients admitted in Intensive care unit, Govt. Rajaji Hospital Madurai.

The study was conducted in 200 ICU patients; the patients had Euvolemic hyponatremia diagnosed by clinical background and further evaluated and confirmed with biochemical and radiological investigations.

The patients are examined clinically with the following parameters and only 200 patients are taken for study.

LABORATORY INVESTIGATIONS DONE

- Serum Sodium, S. Potassium
- CBC
- Blood sugar
- RFT
- Serum Osmolality
- Serum uric acid
- Urine Routine Examination
- Urine Osmolality
- Urine Sodium, Urine Potassium
- Fasting lipid profile,Serum protein if needed
- CXR,CT-Chest,CT-brain if needed
- Thyroid function tests, Serum Cortisol if needed

STEP 1 – Serum Osmolality

Serum Osmolality,(mosm/kg)

=(2 x Na+) + (glucose/18) + (BUN/2.8)

- Hypertonic – (>295)

  Hyperglycemia, Mannitol, Glycerol

- Isotonic – (280-295)

  Pseudo-hyponatremia from elevated lipids or protein

- Hypotonic – (<280)

  Excess fluid intake, Low solute intake, Renal disease, SIADH,Hypothyroidism, Adrenal insufficiency, CHF, Cirrhosis.

STEP 2 –Volume Status

Second Assess volume status (extracellular fluid volume)

Hypotonic hyponatremia has 3 main Etiologies,

- ❖ Hypovolemic – both water and Na decreased (H20 < Na)
  Diarrhea, Vomiting,Dehydration, Malnutrition, etc

- ❖ Euvolemic – water increased and Na stable
  SIADH, Thyroid disease, Primary polydipsia

- ❖ Hypervolemic – Both water increased , Na increased (H2O > Na)
  CHF, cirrhosis, renal failure.

STEP 3 – Urine Studies

For Euvolemic hyponatremia, check urine osmolality,

- ✓ Urine osmolality <100 - Excess water intake
  - o Primary polydipsia, Tap water enemas, Post TURP

- ✓ Urine osmolality >100 - Impaired renal concentration
  - o SIADH, Hypothyroidism, Cortisol deficiency

Check urine sodium & calculate FeNa %

- ✓ Low urine sodium (<20) and low FeNa (<1%) implies the kidneys are appropriately reabsorbing sodium

- ✓ High urine sodium (>20) and high FeNa (>1%) implies the kidneys are not functioning properly.

Criteria for Diagnosing SIADH

- ✓ Decreased effective osmolality of the extracellular fluid.
- ✓ Inappropriate urinary concentration (Uosm >100 mOsmol/kg H2O) with normal renal function) at some level of plasma hypoosmolality.
- ✓ Clinical euvolemia.
- ✓ Elevated urinary sodium excretion (>20 mmol/L) while on normal salt and water intake.
- ✓ Absence of other potential causes of euvolemic hypo-osmolality
- ✓ Normal renal,adrenal and thyroid function and absence of diuretic use, particularly thiazide diuretics.

Others are,

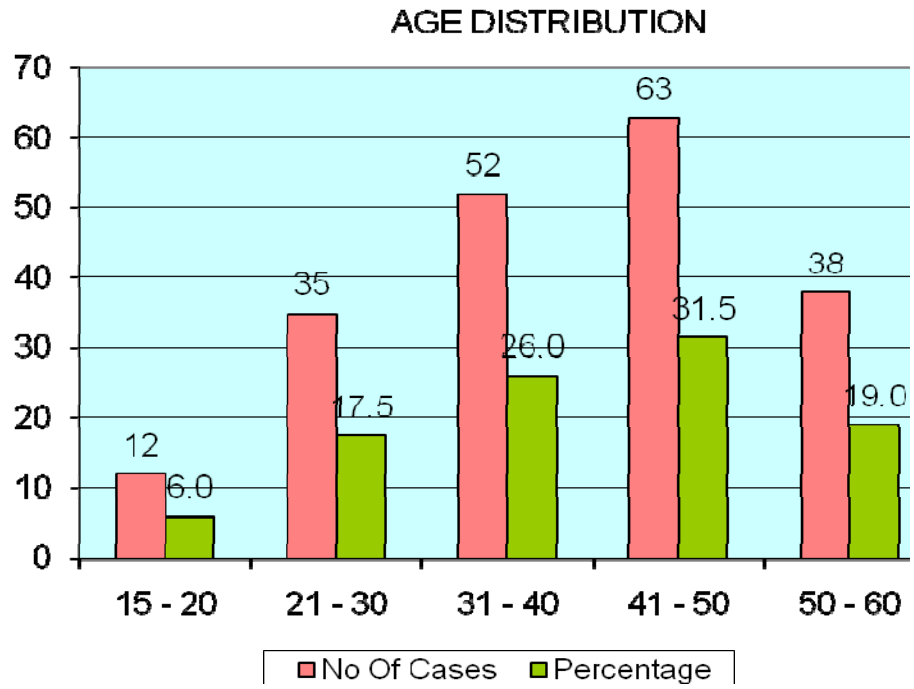
-Low blood urea nitrogen,less than 10 mg/dl;

-Hypourecemia less than 4 mg/dl;

From these things,hypervolemic and hypovolemic hyponatremia are excluded,and only 200 Euvolemic hypontremia patients are selected and assessed

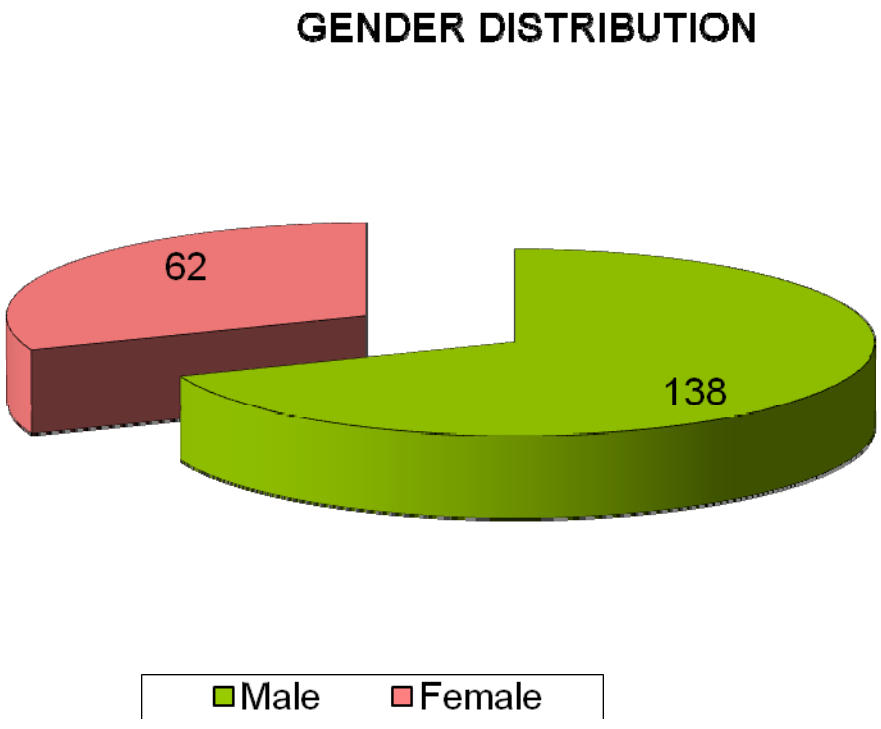
RESULTS AND INTERPRETATION

AGE	NO OF CASES	PERCENTAGE
15 - 20	12	6.0
21 - 30	35	17.5
31 - 40	52	26.0
41 - 50	63	31.5
51 - 60	38	19.0
Total	200	100.0



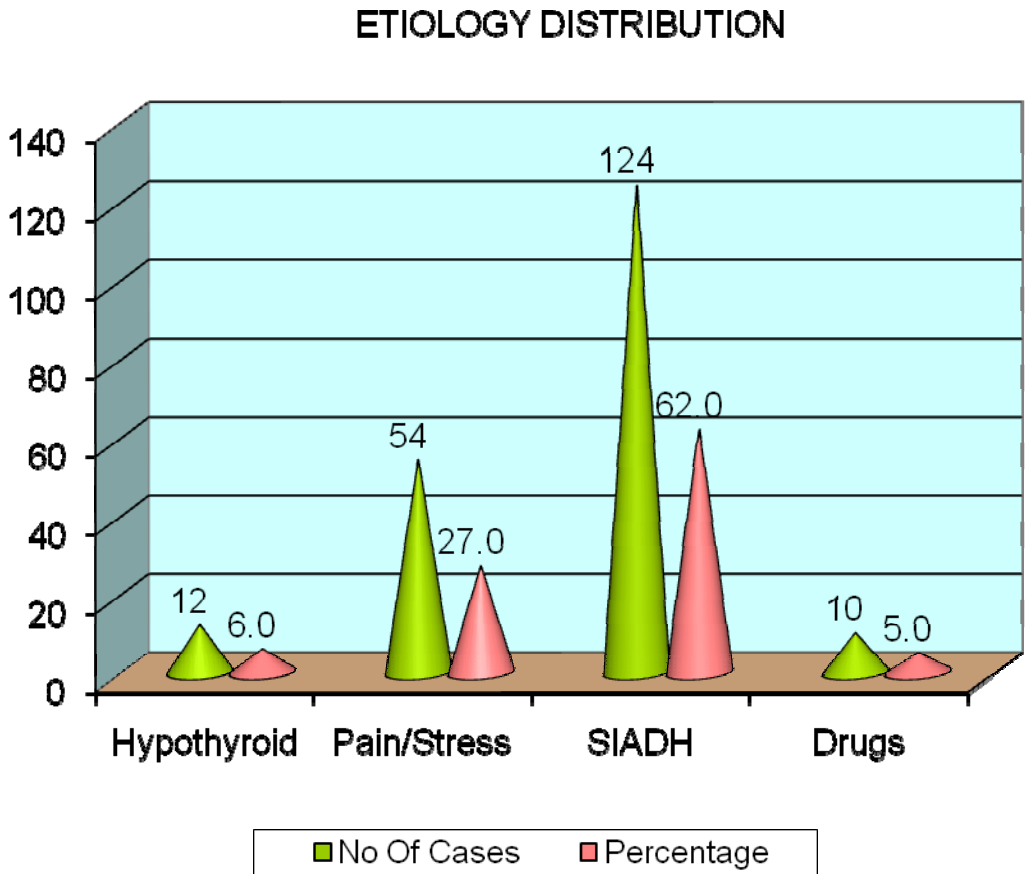
The more number of patients belongs to the age group of 31 to 50 ,57.5%..Among this group ,41 to 50 yrs patients are more common .so more prevalent in middle age group.

SEX	NO OF CASES	PERCENTAGE
Male	138	69.0
Female	62	31.0
Total	200	100.0



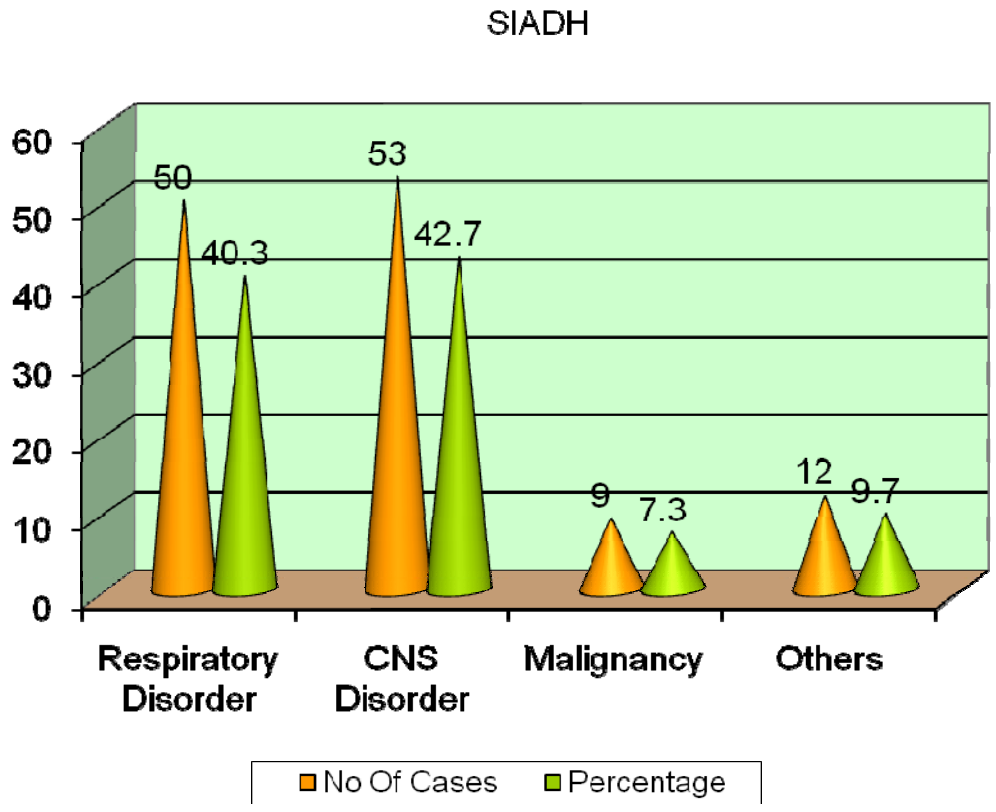
Out of 200 patients,Male 138 (69%),Female patients 62 (31%).More prevalent in male patients comparing with female patients.

ETIOLOGY	NO OF CASES	PERCENTAGE
Hypothyroid	12	6.0
Pain/Stress	54	27.0
SIADH	124	62.0
Drugs	10	5.0
Total	200	100.0



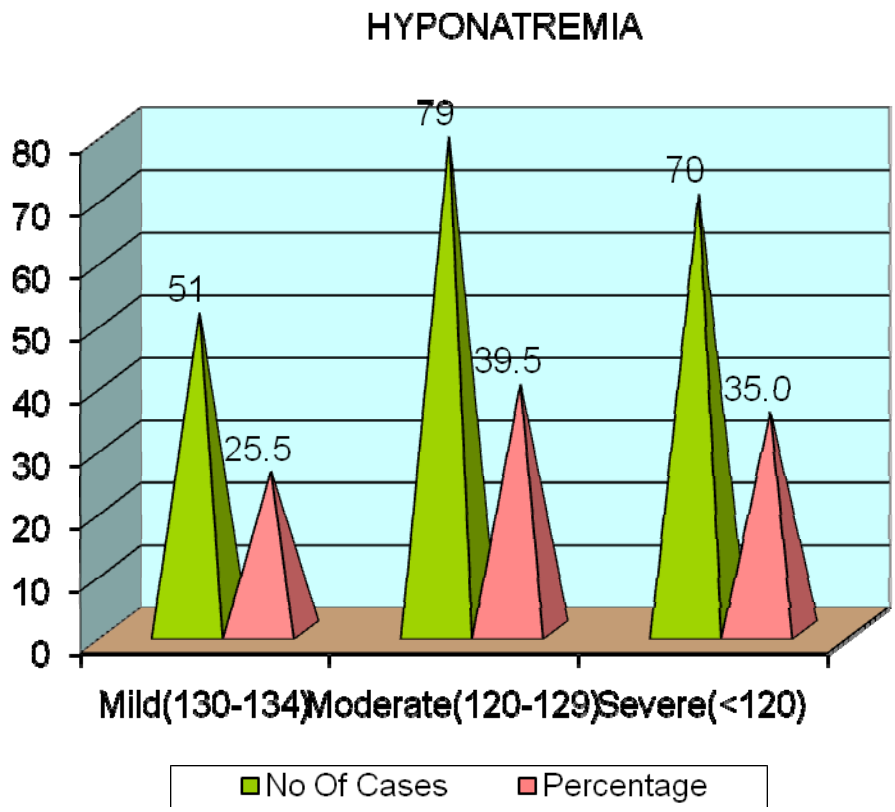
SIADH Contributes 62%,followed by Pain/Stress which contributes 27%.Both contribute 89%

SIADH	NO OF CASES	PERCENTAGE
Respiratory Disorder	50	40.3
CNS Disorder	53	42.7
Malignancy	9	7.3
Others	12	9.7
Total	124	100.0



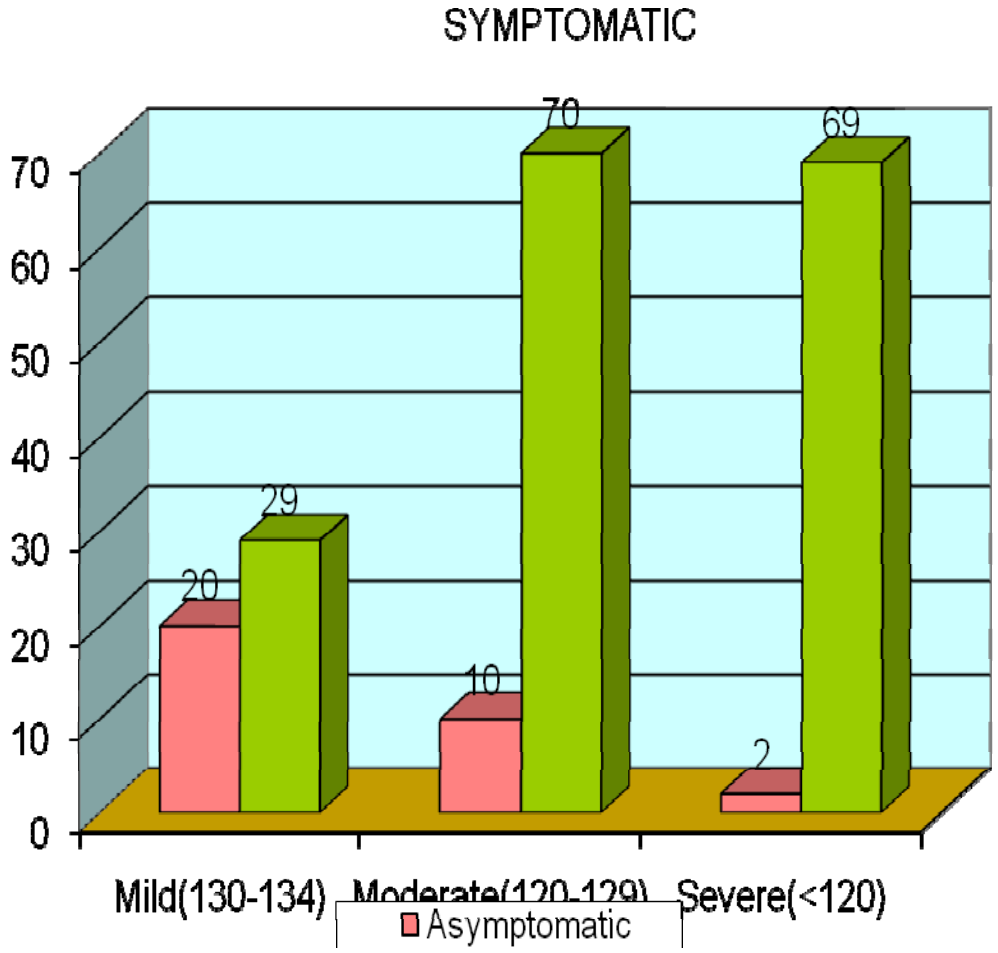
Among SIADH,CNS Disorders contributes 42.7% and Respiratory disorders contributes 40.3% . Both disorders contributes 83%.

HYPONATREMIA	NO OF CASES	PERCENTAGE
Mild(130-134)	51	25.5
Moderate(120-129)	79	39.5
Severe(<120)	70	35.0
Total	200	100.0



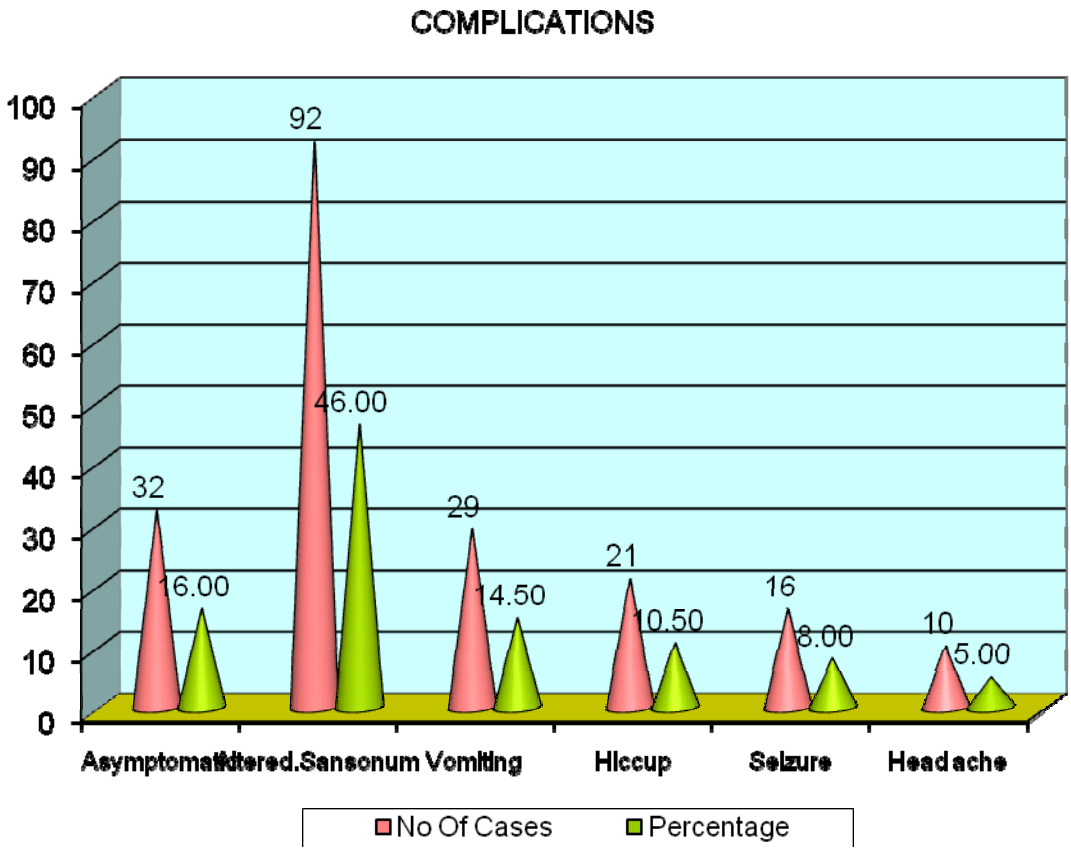
Moderate hyponatremia 39.5 % followed by severe hyponatremia 35%

	ASYMPTOMATIC	SYMPTOMATIC	TOTAL		
Mild(130-134)	20	29	49		
Moderate(120-129)	10	70	80	<0.001	Significant
Severe(<120)	2	69	71	<0.001	Significant
Total	32	168	200		



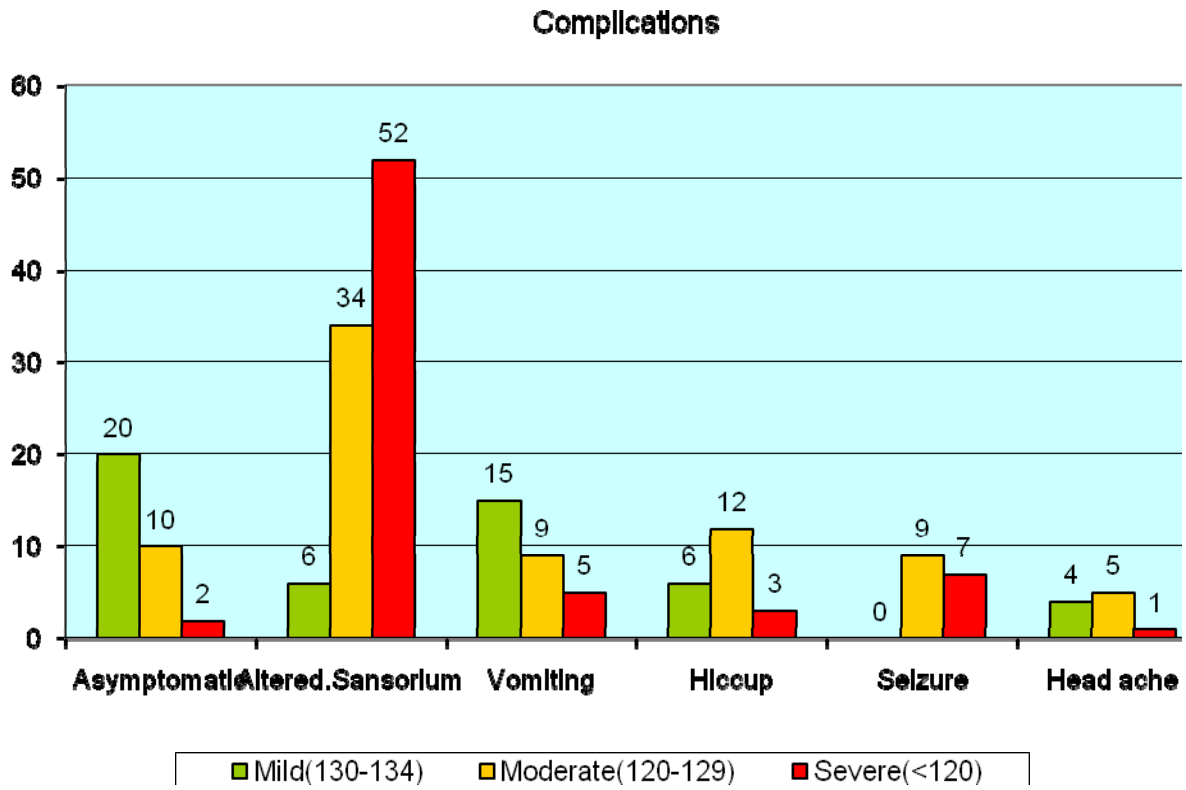
Moderate and severe hyponatremia,both have significant morbidity.

	NO OF CASES	PERCENTAGE
Asymptomatic	32	16.00
Altered Sensorium	92	46.00
Vomiting	29	14.50
Hiccup	21	10.50
Seizure	16	8.00
Head ache	10	5.00
Total	200	100.00



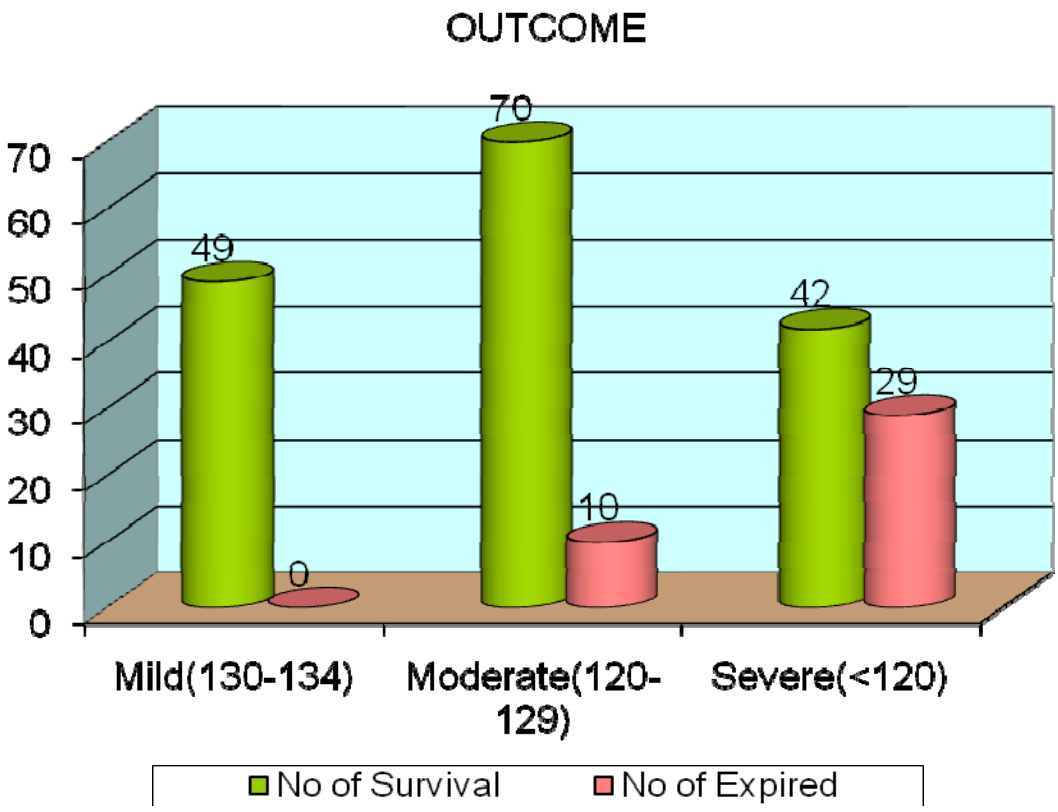
Among complications,Altered sensorium more common (46%),followed by Vomiting(14.5%),Hiccup(10.5%).

	Mild(130-134)	Moderate(120-129)	Severe(<120)	Total
Asymptomatic	20	10	2	32
Altered.Sensorium	6	34	52	92
Vomiting	15	9	5	29
Hiccup	6	12	3	21
Seizure	0	9	7	16
Head ache	4	5	1	10
Total	51	79	70	200



Altered sensorium and seizure more common in severe group,59 out of 70. Altered sensorium,vomiting hiccup and seizure more common in moderate group,64 out of 79.

OUTCOME	NO OF SURVIVAL	NO OF EXPIRED	TOTAL
Mild(130-134)	49	0	49
Moderate(120-129)	70	10	80
Severe(<120)	42	29	71
Total	161	39	200
	P value	<0.001	Significant



Moderate and severe hyponatremia,both have significant mortality.

DISCUSSION

Hyponatremia is a common electrolyte abnormality seen in hospitalized patients.The hypovolemic hyponatremia and hypervolemic hyponatremia are excluded,only euvolemic hyponatremia patients are examined and assessed.

In this study, the more number of patients belongs to the age group of 31 to 50 yrs,(57.5%).Among this group ,41 to 50 yrs patients are more common . 51 to 60 yrs contributes 19%. so euvolemic hyponatremia more prevalent in middle age group comparing with younger age groups.

In this study,Out of 200 patients,Male 138 (69%),Female patients 62 (31%). So Euvolemic hyponatremia more prevalent in male patients comparing with female patients.

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In this study ,SIADH Contributes 62%,followed by Pain/Stress which contributes 27%.Both contribute 89%,Hypothyroid 6%and drugs 5%. .Among SIADH,CNS Disorders contributes 42.7% and Respiratory disorders contributes 40.3% . Both disorders contributes 83%,followed by malignancy(7.3%) and others (9.7%).

Number of patients in Moderate hyponatremia 39.5 % followed by severe hyponatremia 35%,so more numbers of euvolemic patients (74.5%) had developed significant hyponatremia

Out of 200 euvolemic hyponatremia patients,168 patients symptomatic and 32 patients asymptomatic. Asymptomatic patients more in mild groups(20 out of 32), Symptomatic patients more in moderate and severe groups(139 out of 168). So Moderate and severe euvolemic hyponatremia,both have significant morbidity.

Among complications,Altered sensorium more common (46%),followed by Vomiting(14.5%), Hiccup(10.5%), seizure(8%) and headach(5%), Asymptomatic(16%) .Altered sensorium and seizure more common in severe group,(59 out of 70). Altered sensorium,vomiting hiccup and seizure more common in moderate group,(64 out of 79).Vomiting (15) more common in mild groups,and Asymptomatic patients (20) more in mild groups.

In this study,in severe hyponatremia group had more number of death (29 out of 71),followed by moderate hyponatremia (10 out of 80). So Moderate and severe hyponatremia,both have significant mortality.

Early recognition of hyponatremia and appropriate intervention will improve the outcome of icu patients.

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LIMITATIONS OF THIS STUDY

- ✓ Only euvolemic hyponatremia patients
- ✓ Treatment and prognosis part not included
- ✓ Smaller study population
- ✓ Less duration of study
- ✓ No control group in this study

CONCLUSSION

- ❖ Hyponatremia is commonly encountered electrolyte imbalance in icu patients
- ❖ Morbidity and mortality is significantly higher in patients with hyponatremia
- ❖ Early recognisation and timely intervention of hyponatremia will improve the outcome
- ❖ Hyponatremia as an independent prognostic factor for predicting the morbidity and mortality of Icu patients who are having euvolemic hyponatremia.

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PATIENT PROFORMA

Name:

Age/ Sex:

IP.No:

Occupation:

Presenting complaints:

Past history:

H/O Diabetes, Systemic Hypertension, Chronic liver disease, Coronary artery disease, Chronic kidney disease,Thyroid disoreder,Pulmonary tuberculosis.

H/O Any drug intake in the past

Personal history:

Alcohol consumption

Smoking

Diet habits

General Examination

Vitals

BP

Pulse rate

RR

SpO2

System Examination

CVS:

RS:

Abdomen:

CNS:

LABORATORY INVESTIGATION

- Serum Sodium, S. Potassium
- CBC
- Blood sugar
- RFT
- Serum Osmolality
- Serum uric acid
- Urine Routine Examination
- Urine Osmolality
- Urine Sodium, Urine Potassium
- Fasting lipid profile,Serum protein if needed
- CXR,CT-Chest,CT-brain if needed
- Thyroid function tests, Serum Cortisol if needed.

ABBREVIATIONS

AVP-Arginine vasopressin

ADH-Anti diurectic hormone

ICU-Intensive care unit

AQP1-aquaporin 1

ECF-Extra cellular fluid

TRPV-transient receptor potential vallinoid family

CHF -Congestive heart failure

SIADH-The syndrome of inappropriate antidiuresis hormone

TCA -Tricyclic Antidepressants

SSRIs- Selective serotonin reuptake inhibitors

Na^+ -Sodium

Cl^- -Chloride

K^+ -Potassium

BUN -Blood urea nitrogen

ODS-osmotic demyelination syndrome

GFR- Glomerular Filtration Rate

DDAVP- desmopressin acetate

CKD-Chronic kidney disease

CAD-Coronary artery disease

CBC –Complete blood count

RFT Renal function test

CXR-Chest x-ray

S.No.	Age	Sex	Etiology	Disease	Hyponatremia	Hyponatremia	symptomatic/ Asymptomatic	Clinical manifestations	Outcome
1	35	M	SIADH	CNS disorder	124	Moderate	Symptomatic	Altered.Sensorium	survival
2	42	F	SIADH	Others	132	Mild	symptomatic	Altered.Sensorium	survival
3	32	M	Hypothyroid		121	Moderate	symptomatic	Hiccup	survival
4	29	M	Pain/Stress		120	Moderate	symptomatic	Altered.Sensorium	survival
5	45	F	SIADH	Respiratory Disorder	123	Moderate	Asymptomatic	Asymptomatic	survival
6	20	M	SIADH	Malignancy	131	Mild	symptomatic	Head ache	survival
7	41	M	Drugs		119	Severe	symptomatic	Altered.Sensorium	survival
8	35	M	Pain/Stress		125	Moderate	symptomatic	Seizure	survival
9	27	F	Pain/Stress		132	Mild	symptomatic	Vomitting	survival
10	46	M	SIADH	Respiratory Disorder	122	Moderate	symptomatic	Head ache	survival
11	39	M	Pain/Stress		122	Moderate	symptomatic	Vomitting	survival
12	24	F	Drugs		133	Mild	Asymptomatic	Asymptomatic	survival
13	60	M	Hypothyroid		115	Severe	symptomatic	Altered.Sensorium	Expired
14	37	M	SIADH	CNS disorder	125	Moderate	symptomatic	Altered.Sensorium	Expired
15	26	F	Pain/Stress		113	Severe	symptomatic	Altered.Sensorium	survival
16	47	M	SIADH	Respiratory Disorder	134	Mild	symptomatic	Vomitting	survival
17	51	M	Pain/Stress		124	Moderate	Asymptomatic	Asymptomatic	survival
18	58	F	SIADH	CNS disorder	123	Moderate	symptomatic	Hiccup	survival
19	22	M	Pain/Stress		130	Mild	Asymptomatic	Asymptomatic	survival
20	52	F	SIADH	Others	126	Moderate	symptomatic	Altered.Sensorium	survival
21	35	M	Pain/Stress		114	Severe	symptomatic	Hiccup	survival
22	18	F	SIADH	Respiratory Disorder	134	Mild	symptomatic	Hiccup	survival
23	48	M	SIADH	CNS disorder	118	Severe	symptomatic	Altered.Sensorium	Expired
24	38	M	Hypothyroid		123	Moderate	symptomatic	Altered.Sensorium	survival
25	38	M	SIADH	CNS disorder	131	Mild	symptomatic	Altered.Sensorium	survival
26	34	M	Pain/Stress		113	Severe	symptomatic	Seizure	survival
27	43	F	SIADH	Respiratory Disorder	125	Moderate	symptomatic	Vomitting	survival
28	38	F	SIADH	CNS disorder	114	Severe	Asymptomatic	Asymptomatic	survival

29	22	M	Pain/Stress		132	Mild	Asymptomatic	Asymptomatic	survival
30	35	F	SIADH	Others	128	Moderate	symptomatic	Head ache	survival
31	59	M	Pain/Stress		118	Severe	symptomatic	Altered.Sensorium	Expired
32	49	M	SIADH	Respiratory Disorder	131	Mild	symptomatic	Vomitting	survival
33	34	F	SIADH	Malignancy	124	Moderate	symptomatic	Hiccup	survival
34	36	M	Hypothyroid		114	Severe	symptomatic	Altered.Sensorium	survival
35	46	M	SIADH	Respiratory Disorder	133	Mild	Asymptomatic	Asymptomatic	survival
36	15	F	SIADH	CNS disorder	126	Moderate	Asymptomatic	Asymptomatic	survival
37	34	M	Pain/Stress		113	Severe	symptomatic	Vomitting	survival
38	50	M	SIADH	Respiratory Disorder	120	Moderate	symptomatic	Altered.Sensorium	Expired
39	47	F	Pain/Stress		118	Severe	symptomatic	Altered.Sensorium	Expired
40	24	F	SIADH	CNS disorder	112	Severe	symptomatic	Seizure	survival
41	48	M	SIADH	Respiratory Disorder	127	Moderate	symptomatic	Seizure	survival
42	35	F	Drugs		123	Moderate	symptomatic	Altered.Sensorium	survival
43	45	M	SIADH	Others	117	Severe	symptomatic	Altered.Sensorium	Expired
44	39	M	SIADH	CNS disorder	134	Mild	symptomatic	Hiccup	Expired
45	28	F	SIADH	Respiratory Disorder	115	Severe	symptomatic	Altered.Sensorium	survival
46	49	M	Hypothyroid		117	Severe	symptomatic	Altered.Sensorium	survival
47	35	M	SIADH	CNS disorder	129	Moderate	symptomatic	Vomitting	survival
48	52	F	Pain/Stress		112	Severe	symptomatic	Altered.Sensorium	Expired
49	39	M	SIADH	Malignancy	111	Severe	symptomatic	Altered.Sensorium	survival
50	50	F	SIADH	Respiratory Disorder	128	Moderate	Asymptomatic	Asymptomatic	survival
51	58	M	Drugs		122	Moderate	symptomatic	Altered.Sensorium	survival
52	35	F	SIADH	Others	133	Mild	Asymptomatic	Asymptomatic	survival
53	35	M	SIADH	CNS disorder	115	Severe	symptomatic	Altered.Sensorium	Expired
54	53	M	Pain/Stress		125	Moderate	symptomatic	Altered.Sensorium	survival
55	16	M	SIADH	Respiratory Disorder	113	Severe	symptomatic	Altered.Sensorium	Expired
56	46	M	SIADH	CNS disorder	134	Mild	Asymptomatic	Asymptomatic	survival
57	37	F	SIADH	Others	124	Moderate	symptomatic	Altered.Sensorium	survival
58	36	F	Drugs		123	Moderate	symptomatic	Hiccup	survival
59	41	M	SIADH	Respiratory Disorder	130	Mild	symptomatic	Vomitting	survival
60	25	F	SIADH	CNS disorder	126	Moderate	symptomatic	Altered.Sensorium	Expired
61	43	M	Hypothyroid		114	Severe	symptomatic	Head ache	survival
62	57	M	SIADH	CNS disorder	134	Mild	symptomatic	Head ache	survival
63	39	F	SIADH	Respiratory Disorder	118	Severe	symptomatic	Altered.Sensorium	Expired
64	54	M	SIADH	CNS disorder	123	Moderate	symptomatic	Head ache	survival

65	27	M	SIADH	Respiratory Disorder	131	Mild	Asymptomatic	Asymptomatic	survival
66	47	F	Pain/Stress		113	Severe	symptomatic	Seizure	Expired
67	38	M	SIADH	CNS disorder	125	Moderate	symptomatic	Seizure	survival
68	55	M	SIADH	Malignancy	114	Severe	symptomatic	Altered.Sensorium	survival
69	37	F	Drugs		120	Moderate	symptomatic	Altered.Sensorium	survival
70	17	F	SIADH	Respiratory Disorder	128	Moderate	Asymptomatic	Asymptomatic	survival
71	42	M	Pain/Stress		118	Severe	symptomatic	Altered.Sensorium	Expired
72	36	F	SIADH	CNS disorder	131	Mild	symptomatic	Vomitting	survival
73	48	M	SIADH	CNS disorder	124	Moderate	symptomatic	Vomitting	survival
74	56	M	SIADH	Respiratory Disorder	114	Severe	symptomatic	Vomitting	survival
75	26	F	SIADH	Others	132	Mild	Asymptomatic	Asymptomatic	survival
76	54	M	Pain/Stress		118	Severe	symptomatic	Altered.Sensorium	Expired
77	42	F	SIADH	CNS disorder	112	Severe	symptomatic	Altered.Sensorium	survival
78	35	F	SIADH	Respiratory Disorder	127	Moderate	symptomatic	Seizure	survival
79	23	M	SIADH	CNS disorder	123	Moderate	symptomatic	Hiccup	Expired
80	43	M	Hypothyroid		117	Severe	symptomatic	Hiccup	Expired
81	39	F	SIADH	CNS disorder	134	Mild	Asymptomatic	Asymptomatic	survival
82	18	M	SIADH	Respiratory Disorder	115	Severe	symptomatic	Altered.Sensorium	survival
83	44	M	Drugs		117	Severe	symptomatic	Altered.Sensorium	survival
84	34	F	Pain/Stress		129	Moderate	symptomatic	Altered.Sensorium	survival
85	55	M	SIADH	CNS disorder	112	Severe	symptomatic	Seizure	Expired
86	26	M	SIADH	Malignancy	111	Severe	symptomatic	Altered.Sensorium	survival
87	53	M	SIADH	Respiratory Disorder	128	Moderate	symptomatic	Altered.Sensorium	survival
88	59	F	SIADH	CNS disorder	122	Moderate	symptomatic	Hiccup	survival
89	41	M	Pain/Stress		133	Mild	symptomatic	Hiccup	survival
90	32	F	SIADH	CNS disorder	115	Severe	symptomatic	Altered.Sensorium	survival
91	58	F	SIADH	Respiratory Disorder	125	Moderate	Asymptomatic	Asymptomatic	survival
92	25	M	SIADH	CNS disorder	113	Severe	symptomatic	Altered.Sensorium	Expired
93	45	M	Pain/Stress		134	Mild	Asymptomatic	Asymptomatic	survival
94	22	M	SIADH	Respiratory Disorder	124	Moderate	symptomatic	Altered.Sensorium	survival
95	46	M	SIADH	Others	123	Moderate	symptomatic	Altered.Sensorium	Expired
96	40	F	SIADH	Respiratory Disorder	124	Moderate	symptomatic	Altered.Sensorium	survival
97	56	M	SIADH	CNS disorder	132	Mild	symptomatic	Altered.Sensorium	survival
98	23	F	Pain/Stress		121	Moderate	symptomatic	Head ache	survival
99	46	F	SIADH	Respiratory Disorder	118	Severe	symptomatic	Altered.Sensorium	survival

100	35	M	SIADH	CNS disorder	123	Moderate	symptomatic	Vomitting	survival
101	47	M	Hypothyroid		131	Mild	Asymptomatic	Asymptomatic	survival
102	54	M	SIADH	CNS disorder	119	Severe	symptomatic	Altered.Sensorium	survival
103	44	M	SIADH	Respiratory Disorder	125	Moderate	symptomatic	Seizure	survival
104	16	M	SIADH	CNS disorder	132	Mild	symptomatic	Vomitting	survival
105	31	F	Pain/Stress		122	Moderate	Asymptomatic	Asymptomatic	survival
106	51	M	SIADH	Respiratory Disorder	122	Moderate	symptomatic	Altered.Sensorium	survival
107	25	M	SIADH	CNS disorder	133	Mild	Asymptomatic	Asymptomatic	survival
108	52	M	SIADH	Respiratory Disorder	115	Severe	symptomatic	Vomitting	Expired
109	43	M	SIADH	Malignancy	125	Moderate	symptomatic	Altered.Sensorium	Expired
110	24	F	Pain/Stress		113	Severe	symptomatic	Altered.Sensorium	survival
111	36	F	SIADH	Respiratory Disorder	134	Mild	symptomatic	Vomitting	Expired
112	21	M	SIADH	Respiratory Disorder	124	Moderate	symptomatic	Hiccup	survival
113	47	M	Hypothyroid		123	Moderate	symptomatic	Altered.Sensorium	survival
114	40	M	SIADH	CNS disorder	130	Mild	symptomatic	Vomitting	survival
115	49	F	SIADH	CNS disorder	126	Moderate	symptomatic	Altered.Sensorium	survival
116	30	M	SIADH	Respiratory Disorder	118	Severe	symptomatic	Altered.Sensorium	Expired
117	41	F	SIADH	CNS disorder	123	Moderate	symptomatic	Seizure	survival
118	56	M	Pain/Stress		131	Mild	Asymptomatic	Asymptomatic	survival
119	19	M	SIADH	Respiratory Disorder	113	Severe	symptomatic	Seizure	survival
120	48	M	SIADH	Others	125	Moderate	symptomatic	Vomitting	survival
121	37	M	SIADH	Respiratory Disorder	114	Severe	symptomatic	Altered.Sensorium	survival
122	54	F	SIADH	Respiratory Disorder	132	Mild	symptomatic	Vomitting	survival
123	48	M	Pain/Stress		128	Moderate	symptomatic	Altered.Sensorium	survival
124	52	F	SIADH	CNS disorder	118	Severe	symptomatic	Altered.Sensorium	Expired
125	59	M	SIADH	Respiratory Disorder	131	Mild	symptomatic	Hiccup	survival
126	42	M	Pain/Stress		124	Moderate	Asymptomatic	Asymptomatic	survival
127	34	M	SIADH	CNS disorder	114	Severe	symptomatic	Altered.Sensorium	survival
128	24	M	Pain/Stress		133	Mild	Asymptomatic	Asymptomatic	survival
129	47	M	SIADH	Respiratory Disorder	126	Moderate	symptomatic	Altered.Sensorium	Expired
130	39	M	Pain/Stress		113	Severe	symptomatic	Altered.Sensorium	survival
131	52	F	SIADH	Respiratory Disorder	132	Mild	symptomatic	Altered.Sensorium	survival
132	18	F	SIADH	Respiratory Disorder	118	Severe	symptomatic	Altered.Sensorium	survival
133	32	M	Hypothyroi		112	Severe	symptomatic	Vomitting	Expired

			d						
134	49	M	SIADH	CNS disorder	127	Moderate	symptomatic	Hiccup	survival
135	46	M	Pain/Stress		123	Moderate	symptomatic	Altered.Sensorium	survival
136	21	M	SIADH	CNS disorder	117	Severe	symptomatic	Altered.Sensorium	survival
137	56	F	Pain/Stress		134	Mild	symptomatic	Head ache	survival
138	44	M	Drugs		115	Severe	symptomatic	Altered.Sensorium	survival
139	29	M	SIADH	Respiratory Disorder	132	Mild	symptomatic	Vomitting	survival
140	57	M	Pain/Stress		121	Moderate	symptomatic	Altered.Sensorium	survival
141	45	F	Pain/Stress		115	Severe	symptomatic	Seizure	survival
142	34	F	SIADH	CNS disorder	123	Moderate	symptomatic	Hiccup	survival
143	38	M	SIADH	Respiratory Disorder	131	Mild	Asymptomatic	Asymptomatic	survival
144	50	M	Pain/Stress		119	Severe	symptomatic	Hiccup	Expired
145	26	M	SIADH	Respiratory Disorder	125	Moderate	symptomatic	Seizure	survival
146	49	M	SIADH	Respiratory Disorder	132	Mild	symptomatic	Vomitting	survival
147	20	M	Pain/Stress		122	Moderate	symptomatic	Vomitting	survival
148	56	M	SIADH	Malignancy	122	Moderate	symptomatic	Altered.Sensorium	survival
149	38	M	Drugs		133	Mild	symptomatic	Hiccup	survival
150	48	F	SIADH	CNS disorder	115	Severe	symptomatic	Altered.Sensorium	survival
151	43	M	Pain/Stress		125	Moderate	Asymptomatic	Asymptomatic	survival
152	48	M	Pain/Stress		113	Severe	symptomatic	Altered.Sensorium	survival
153	39	M	SIADH	Respiratory Disorder	134	Mild	Asymptomatic	Asymptomatic	survival
154	31	M	SIADH	Others	124	Moderate	symptomatic	Altered.Sensorium	Expired
155	27	M	Pain/Stress		123	Moderate	symptomatic	Altered.Sensorium	survival
156	55	F	SIADH	Respiratory Disorder	130	Mild	symptomatic	Altered.Sensorium	survival
157	42	M	SIADH	CNS disorder	126	Moderate	symptomatic	Hiccup	survival
158	25	M	Pain/Stress		114	Severe	symptomatic	Altered.Sensorium	survival
159	43	M	SIADH	Respiratory Disorder	134	Mild	Asymptomatic	Asymptomatic	survival
160	47	M	SIADH	CNS disorder	118	Severe	symptomatic	Altered.Sensorium	Expired
161	41	M	Hypothyroid		123	Moderate	symptomatic	Altered.Sensorium	survival
162	17	M	Drugs		131	Mild	Asymptomatic	Asymptomatic	survival
163	38	M	SIADH	CNS disorder	113	Severe	Asymptomatic	Asymptomatic	Expired
164	22	M	Pain/Stress		125	Moderate	symptomatic	Seizure	survival
165	51	F	SIADH	CNS disorder	114	Severe	symptomatic	Altered.Sensorium	survival
166	49	M	SIADH	Respiratory Disorder	132	Mild	symptomatic	Vomitting	survival
167	57	M	Pain/Stress		128	Moderate	symptomatic	Vomitting	survival
168	31	M	SIADH	CNS disorder	118	Severe	symptomatic	Altered.Sensorium	Expired
169	41	F	SIADH	Respiratory Disorder	131	Mild	symptomatic	Head ache	survival

170	52	M	Pain/Stress		124	Moderate	symptomatic	Hiccup	survival
171	48	M	Pain/Stress		114	Severe	symptomatic	Altered.Sensorium	survival
172	38	M	SIADH	Malignancy	133	Mild	symptomatic	Vomitting	survival
173	26	M	Pain/Stress		126	Moderate	symptomatic	Head ache	survival
174	47	F	SIADH	Respiratory Disorder	113	Severe	symptomatic	Altered.Sensorium	survival
175	56	M	Pain/Stress		132	Mild	Asymptomatic	Asymptomatic	survival
176	25	M	SIADH	Respiratory Disorder	118	Severe	symptomatic	Altered.Sensorium	Expired
177	46	M	Pain/Stress		112	Severe	symptomatic	Vomitting	survival
178	23	F	SIADH	CNS disorder	127	Moderate	symptomatic	Altered.Sensorium	survival
179	46	M	SIADH	Others	123	Moderate	symptomatic	Altered.Sensorium	survival
180	26	F	Pain/Stress		117	Severe	symptomatic	Altered.Sensorium	survival
181	32	M	SIADH	CNS disorder	134	Mild	symptomatic	Vomitting	survival
182	33	M	Hypothyroid		115	Severe	symptomatic	Altered.Sensorium	Expired
183	45	M	SIADH	CNS disorder	117	Severe	symptomatic	Seizure	Expired
184	59	M	Pain/Stress		129	Moderate	symptomatic	Altered.Sensorium	survival
185	25	M	SIADH	Respiratory Disorder	112	Severe	symptomatic	Altered.Sensorium	survival
186	49	M	SIADH	CNS disorder	111	Severe	symptomatic	Altered.Sensorium	Expired
187	44	F	SIADH	CNS disorder	128	Moderate	Asymptomatic	Asymptomatic	survival
188	21	M	Pain/Stress		122	Moderate	symptomatic	Altered.Sensorium	survival
189	43	F	SIADH	Malignancy	133	Mild	symptomatic	Hiccup	survival
190	39	M	Pain/Stress		115	Severe	symptomatic	Altered.Sensorium	survival
191	35	M	SIADH	CNS disorder	125	Moderate	symptomatic	Vomitting	survival
192	43	M	Pain/Stress		113	Severe	symptomatic	Altered.Sensorium	survival
193	18	F	SIADH	Respiratory Disorder	134	Mild	symptomatic	Altered.Sensorium	survival
194	54	M	Pain/Stress		124	Moderate	symptomatic	Hiccup	survival
195	42	M	SIADH	Others	123	Moderate	symptomatic	Seizure	Expired
196	24	M	Pain/Stress		130	Mild	symptomatic	Vomitting	survival
197	51	M	SIADH	CNS disorder	126	Moderate	symptomatic	Altered.Sensorium	survival
198	41	F	Pain/Stress		114	Severe	symptomatic	Altered.Sensorium	Expired
199	34	M	SIADH	CNS disorder	134	Mild	Asymptomatic	Asymptomatic	survival
200	27	M	SIADH	CNS disorder	118	Severe	symptomatic	Altered.Sensorium	survival

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University,
Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.Mahendran .L
Course	:	PG in MD., General Medicine
Period of Study	:	2016-2019
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Hyponatremia as an independent prognostic factor for morbidity and mortality in ICU patients
Ethical Committee as on	:	10.07.2018

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

DEAN
Madurai Medical College
Madurai-20

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Submitted	2018-10-13 09:35 (+05:0-30)
Submitted by	MAHENDRAN. L (tomahendran.l@gmail.com)
Receiver	tomahendran.l.mgrmu@analysis.urkund.com

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DR. S.RAVINDRAN M.D,
Professor of Medicine,
Chief VIIth Medical unit,
Madurai Medical College &
Govt. Rajaji Hospital,
Madurai .