Evaluation of Serum Markers for Hyponatremia in Patients undergoing Neurosurgery

Dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for the M.Ch. Neurosurgery part II Examination, August 2014

CERTIFICATE

This is to certify that the dissertation entitled — Evaluation of serum markers for hyponatremia in patients undergoing Neurosurgery is the bonafide original work of Dr. Tobin George, Christian medical college, Vellore submitted in partial fulfillment of the rules and regulations, for Branch-II M.Ch. Neurosurgery, Part-II examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in August 2014 under my guidance and supervision during the academic year 2009-2014.

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Evaluation of Serum Markers for Hyponatremia in Patients undergoing Neurosurgery

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September 16, 2011

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Sub: **FLUID Research grant project NEW PROPOSAL**:
Evaluation of a diagnostic protocol in hyponatremia with natriuresis
Dr. Tobin George, Neurological Sciences, Dr. Krishna Prabhu, Dr. Ari G. Chacko, Dr. Mathew Jospeh Neurological Sciences, Dr. Simon Rajaratnam, Endocrinology and Metabolism.

Ref: IRB Min. No 7592 dated 07.09.2011

Dear Dr. George,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Evaluation of a diagnostic protocol in hyponatremia with natriuresis" on September 7, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet (English)
3. Proforma
4. Cvs of Drs. Krishna Prabhu, Ari G. Chacko, Simon Rajaratnam, Mathew Joseph.
5. A CD containing document 1 – 4

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on September 7, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

INSTITUTIONAL REVIEW BOARD (IRB)
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Name	Qualification	Designation	Other Affiliations
Dr. B.J.Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	Non-CMC
Mr. Harikrishnan	BL	Lawyer	Non-CMC
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Academic Officer, CMC	
Dr. Vathsala Sadan (on behalf of Mrs. Rosaline Jayakaran)	M.Sc. (Nursing), RN, RM	Dean, College of Nursing, CMC.	

We approve the project to be conducted as presented.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

A sum of Rs. 80,000/- (Rupees Eighty thousand only) is sanctioned for 2 years.

Yours sincerely,

George Mathew

Dr. George Mathew
Chairman (Research Committee) & Principal
Institutional Review Board

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I owe my gratitude to Dr. Mathew Joseph for granting me permission to continue my study on patients admitted in the Neuro ICU.

I am also grateful to Mr. Selvaraj and Miss Tuny Sebastian from the Department of Biostatistics and Clinical Epidemiology unit who helped with the statistical analysis.

All thanks to God almighty without whom all this would have not been a possibility. I would like to especially thank my wife for all the help, support and encouragement she has given without which I could not have completed this study. I would also like to thank my parents and my in laws who have been a constant support through all my proceedings. My special thanks to all my seniors and juniors who have supported me in this project all this far.

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ABSTRACT

Evaluation of Serum Markers for Hyponatremia in Patients undergoing Neurosurgery

Objective:

We conducted a prospective study to determine the usefulness of serum markers like NT proBNP, Aldosterone, Uric Acid and Antidiuretic hormone (ADH) in differentiating Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) and Cerebral Salt Wasting (CSW) in neurosurgical patients with postoperative hyponatremia with natriuresis (HWN).

Methods:

Hyponatremia was defined as serum Na^+ <130 mEq/l and natriuresis when urine spot sodium was >25mEq/l. 31 non trauma postoperative patients with HWN who met the inclusion criteria were included in our study. In Phase-1, central venous pressure (CVP) greater or less than 5 cm of water was used to differentiate SIADH from CSW in 10 patients with HWN. Based on the values of the serum markers we obtained a "cut-off" value of NT proBNP to distinguish SIADH and CSW. In Phase-2 we used this cut-off value of NT proBNP to treat patients as SIADH or CSW until the serum Na^+ normalized. SIADH was managed with fluid restriction and oral salt. Fluid replacement and oral salt was used for CSW.

Results:

In Phase-1, of 6 patients treated as CSW, 5 patients had an NT proBNP level >125 pg/ml, while of the 4 treated as SIADH, 3 had NT proBNP levels <125 pg/ml. The sensitivity, specificity, positive predictive value and negative predictive value of the NT proBNP assay in this Phase were 83.3%, 75%, 83.3% and 75% respectively. In Phase-2 (21 patients), an NT proBNP cut-off of 125pg/ml accurately diagnosed all 11 patients with SIADH and 9 of 10 patients with CSW, all of whom responded to appropriate therapy. The mean time duration to correct hyponatremia in this Phase was 2.8 ± 1.63 days with a range of 1-8 days. The sensitivity, specificity, positive predictive value and negative predictive value of the NT proBNP assay were 90%, 100%, 100% and 91.67% respectively. Overall the sensitivity, specificity, positive predictive value and negative predictive value of the NT proBNP assay were 87.50%, 93.33%, 93.33% and 87.50% respectively to distinguish SIADH from CSW (p value < 0.001). Aldosterone values were generally low in HWN.

Conclusion:

NT proBNP is a useful serum marker to differentiate SIADH and CSW. Fludrocortisone would be beneficial in both SIADH and CSW. Serum Uric acid levels do not help differentiating SIADH from CSW.

Keywords:

Aldosterone, Antidiuretic hormone, Cerebral Salt Wasting, Hyponatremia, NT proBNP, Syndrome of Inappropriate Antidiuretic hormone secretion, Uric Acid.

AIMS AND OBJECTIVES

To differentiate between the syndrome of inappropriate anti diuretic hormone(SIADH) secretion and cerebral salt wasting(CSW) using serum markers in non traumatic post-operative neurosurgical patients who develop hyponatremia and natriuresis.

INTRODUCTION

Hyponatremia with natriuresis is a notorious entity in postoperative neurosurgical patients which can cause worsening of a patient's neurological status. However hyponatremia has also been detected in asymptomatic patients on routine laboratory testing.[1] The main causes of hyponatremia with natriuresis have been attributed to syndrome of inappropriate anti diuretic hormone (SIADH) or cerebral salt wasting (CSW). While SIADH is associated with hypervolemic, CSW is associated with hypovolemic status. Hence patients with SIADH are treated with fluid restriction while those with CSW are treated with hydration. Studies have attempted to identify the volume status of patients using various clinical, laboratory and invasive (CVP) methods. However none of these methods are foolproof and hence a clear distinction between SIADH and CSW remains elusive.

In our study we chose to look at some serum markers which we hoped would be a less invasive and a more reliable method to distinguish these two entities.

REVIEW OF LITERATURE

Hyponatremia is the most frequent electrolyte imbalance medical practitioners have to deal with.[2] 30% of patients admitted in hospitals have hyponatremia. It is linked with significantly higher death rates over a broad range of primary disorders. The prevalence of hyponatremia in Neurosurgical patients has been reported as high as 50%. [2] The incidence of postoperative hyponatremia in general has been reported to be between 1% to 5%.[3] In a study by Chung et al[4] over 1088 patients undergoing surgery, 4.4% developed hyponatremia inside 7 days. In their study hyponatremia was more common following organ transplantation, cardio - vascular, gastrointestinal surgery and accident surgery. In neurosurgical patients the incidence is higher in patients with subarachnoid hemorrhage, traumatic brain injury, brain tumors, and after pituitary surgery as compared with those with spinal lesions. Waikar et al[5] in a prospective study on 98,411 patients have shown that patients with hyponatremia had elevated mortality rates in hospital at 1 and 5 years. This was even seen in those with mild hyponatremia (130-134 mEq/L).[5] Hyponatremia causes cerebral complications like brain edema, altered sensorium, seizures, vasospasm and death.

The etiology of hyponatremia with natriuresis in patients undergoing neurosurgery is primarily due to either SIADH or CSW.[2]

Table 1: Cause of hyponatremia (serum sodium < 130 mmol/l) in 187 cases recorded in the neurosurgical unit of Beaumont Hospital between January 2002 and September 2003. [6]

Pathophysiology	No. of patients (total = 187)	%
SIADH	116/187	62
Hypovolemia	50/187	26.7
Inappropriate iv fluids	7/187	3.7
CSWS	9/187	4.8
SIADH/CSWS	5/187	2.7

Mild hyponatremia is defined as a serum sodium of 125 - 129 mEq/L. Moderate hyponatremia is defined as a serum sodium ranging from 120 - 124 mEq/L. Severe hyponatremia is defined as a serum sodium ≤ 119 mEq/L.[1]

Clinical Features

The clinical symptomatology is due to brain edema, raised intracranial pressure and cerebral hypoxia.[7] Once the extracellular sodium levels fall following hyponatremia, water from the extracellular compartment flows into the intracellular compartment causing brain edema. The brain responds to this by expelling solutes from both compartments with accompanying water loss which in turn reduces intracerebral edema. [8]

Early symptoms of hyponatremia include apathy, weakness, muscular cramps, nausea, vomiting, and headache. Later these patients develop impaired response to verbal and painful stimuli, hallucinations, urinary incontinence, and pulmonary edema. When the edema progresses, they develop varying degrees of raised intracranial tension and causing the brain to herniate. These may present with decorticate posturing, hypothermia and hyperthermia, central diabetes insipidus and mellitus, seizures, respiratory arrest, coma, permanent brain damage, and death. In a study of 740 patients by Ayus and Arieff [3], the frequency of hyponatremic encephalopathy was 8% with a morbidity rate of 52%. Increased intracranial tension and brain surgery tend to exacerbate the symptoms of hyponatremia. Many patients in Neurosurgical ICU's also have acidosis, hypoxia, or hypercapnia. [9]

Acute hyponatremia

Acute hyponatremia which develops in less than 48 hours causes grave symptoms. This is due to the limited time available for the brain to reduce the edema setting in before the brain herniates due to the volume constraints imposed by a rigid cranium. This could result in Cheyne-Stokes respiration, seizures, coma and herniation of the brainstem.[8]

Chronic hyponatremia

Here hyponatremia takes more than 48 hours to develop giving the brain sufficient time to set in adaptive mechanism to reduce cerebral edema. These patients therefore present with milder symptoms in the form of gait instability, falls, attention deficits and increased risk of fracture.[8]

Based on the time gap between the neurological injury and the onset of hyponatremia Vingerhoets and de Tribolet[10] classified hyponatremia into an acute syndrome (< 3 days) and the delayed syndrome (> 1 week). Antidiuretic hormone levels were found to be raised in the first 3 days and thereafter the levels normalized or were depressed. They felt that the initial surge in the levels of ADH were appropriate rather than inappropriate and the hyponatremia resulting from this should be managed by fluid restriction while that of the chronic syndrome should be managed with salt and fluid supplementation as these were likely to be caused by CSW.

Management of Water Equilibrium

In normal individuals water intake depends on the serum osmolality which in turn is linked to the connection between antidiuretic hormone and thirst sensation. Dedicated neurons situated in the circumventricular organs of the hypothalamus are stimulated by elevations of plasma osmolality. This in turn stimulates production of ADH from the paraventricular and supraoptic nuclei. Neurosecretory granules located in the hypothalamus transport ADH for storage in the posterior pituitary where it will be released into the bloodstream on depolarization of osmoreceptors. ADH thus released in the bloodstream binds to V2 receptors in the collecting duct resulting in reabsorption of water from the urine via a mechanism involving aquaporin 2 terminals located on the luminal surface of the collecting duct.[11] At the same time, a stimulus from the thirst centre of the brain encourages the individual to consume more water. Plasma osmolality and water intake are thus regulated by a combination of restricted water output mediated by ADH and increased water intake mediated by thirst. [9]

Role of intravenous fluids in the pathogenesis of postoperative hyponatremia

In postsurgical patients, arginine vasopressin (AVP) levels are universally increased when compared with preoperative values. Despite abnormalities in AVP metabolism or renal function, hyponatremia does not develop unless excess free water is administered. Approximately 1% of patients develop hyponatremia postoperatively, and symptomatic hyponatremia occurs in approximately 20% of these patients. Following surgery some patients lose the ability to maintain their water equilibrium. In these patients even a relatively small quantity of 3 to 4 liters of intravenous hypotonic fluid over 2 days can alter the plasma osmolality and serum sodium levels resulting in fatal hyponatremic encephalopathy postoperatively.[3] Choice of fluids thus is of paramount importance in postoperative patients.[3]

TYPES OF HYPONATREMIA

Plasma osmolality is normally sustained between 280 and 295 mOsm/kg by ADH. “Effective” solutes are those which are impervious to the cell membrane and remain with the extracellular fluid. Their concentrations are used to determine hypo-osmolality. Sodium and its allied anions are the major effective plasma solutes and therefore hyponatremia and hypo-osmolality are usually identical. There are however 2 situations where hyponatremia and hypo-osmolality do not coexist.

Pseudo hyponatremia.

Lipids and proteins inhabit a larger plasma volume that a molecule of water. Hence higher quantities of these molecules increases plasma volume and gives a false reading of low serum sodium. However, as the total number of particles in solute remains constant, plasma osmolality remains normal in these cases.

Isotonic or hypertonic hyponatremia.

Serum osmolality is a measure of the total number of effective solutes within a given volume of liquid. Effective solutes apart from sodium when present in higher quantities can increase osmolality of the ECF causing a transfer of water from the ICF to ECF. This in turn causes a dilutional hyponatremia. Glucose is an effective solute and hence hyperglycemia is a known cause of hyponatremia. Prolonged hyperglycemia can cause a glucose induced diuresis leading to hypertonic hyponatremia. In these patients it is better to assess osmolality by directly measuring serum osmolality or by correcting the measured serum sodium for the rise in glucose. Direct measurement of serum osmolality is also used in patients on mannitol or having received radiographic contrast as these constitute effective solutes.[12]

Pathogenesis of Hypotonic Hyponatremia

Plasma osmolality is equal in both ICF and ECF as due to the fact that water can move unhindered across both these compartments. Na^+ within the ECF and K^+ within the ICF are the major determinants of plasma osmolality which is calculated by using the formula given below:

$$OSMECF=OSMICF= \frac{ECF\ solute+ICF\ solute}{body\ water} = \frac{2xNaE+2xKE+nonelectrolyte\ solute}{body\ water}$$

OSMECF= osmolality of extracellular fluid

OSMICF= osmolality of intracellular fluid

The above formula shows us that hypotonic hyponatremia is caused by surplus water in the ECF due to either excess body water or by depletion of either Na or K or both. [12]

TYPES OF HYPOTONIC HYPONATREMIA

Based on a patient's ECF volume status, hyponatremia is classified into hypovolemic, euvolemic, and hypervolemic hyponatremia. An exact measurement of the volume status of an individual is essential for this classification.

Hypovolemic hyponatremia.

In hypovolemic hyponatremia both total body water and total body sodium are decreased and greater decrease in total body sodium leads to hyponatremia. There is loss of sodium from either the kidney or elsewhere. Clinical signs of volume depletion include postural hypotension, increase in heart rate, drying of mucus membranes, reduced skin turgor. These clinical signs are neither sensitive nor specific. Urine spot sodium should be <25 mmol/L in these patients unless the kidney is the site of sodium loss. [12] Causes of extra renal loss of sodium which occurs in these patients include vomiting, diarrhea, pancreatitis, burns, and sweating.

Euvolemic hyponatremia.

In euvolemic hyponatremia total body sodium remains slightly low normal while total body water is increased, leading to hyponatremia. Many different hypo-osmolar disorders can present with SIADH which causes this form of hyponatremia. Patients without clinical signs of volume depletion or volume expansion (subcutaneous edema, ascites) are considered to be euvolemic unless evidence points to an abnormal ECF volume. Urine spot sodium should be ≥25 mmol/L in these patients. [12]

Hypervolemic hyponatremia.

In hypervolemic hyponatremia there is an increase in both total body water and total body sodium. In these patients excretion of body water is decreased causing a dilutional effect on the available serum sodium. Hyponatremia with volume excess in the extracellular space can arise with many diseases. Clinical signs of volume excess include subcutaneous edema, ascites and pulmonary edema. In these patients the urine sodium is usually <25 mmol/L due to activation of the renin-angiotensin-aldosterone system (RAAS) with secondary renal sodium conservation despite the whole-body volume overload. [12]

Table 2: Differential diagnosis of hyponatremia based on urinary spot [Na+][13].

	Urine [Na+] <20 mmol/L	**Urine [Na+] >40 mmol/L**
Hypovolemia (dry tongue, decreased CVP, increased urea,increased pulse, decreased BP)	Vomiting, diarrhea, skin losses, burns	Diuretics, Addison's, cerebral salt-wasting syndrome, salt-losing nephropathy
Euvolemia	Hypothyroidism Any cause + hypotonic fluids	SIADH Glucocorticoid deficiency Drugs
Hypervolemic (edema, ascites, LVF, increased JVP, increased CVP)	CCF, cirrhosis Nephrotic syndrome	Renal failure, any cause + diuretics

BP = blood pressure; CCF = congestive cardiac failure; CVP = central venous pressure; LVF = left ventricular failure; JVP = jugular venous pressure; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

PATHOPHYSIOLOGY OF HYPOTONIC HYPONATREMIA

Hypovolemic Hyponatremia

Gastrointestinal disease

Prolonged vomiting and diarrhea leads to loss of gastric contents and stool (which are hypotonic) ultimately leading to volume depletion and hypernatremia. This stimulates ADH secretion. When patients take in a lot of fluids and food low in sodium in this setting, they develop hyponatremia. Urine spot sodium will be low if the patient has diarrhea or high if the patient has persistent vomiting. [12]

Diuretic therapy

Diuretics cause loss of sodium from the kidneys and adversely affect the ability of distal tubules to dilute urine. Renal excretion of sodium results in a high urine [Na^+] level. Thiazide drugs and furosemide are the most common cause of diuretic induced hyponatremia. [12]

Mineralocorticoid deficiency

Occurs in primary adrenal insufficiency where sodium is lost through the kidneys leading to hypovolemia which then secondarily stimulates AVP release. Volume loss with high urine spot sodium and associated hyperkalemia is indicative of this condition. A low urinary potassium verifies the diagnosis. In these patients corticosteroids must be given immediately even as blood tests to measure cortisol, aldosterone, and ACTH levels are being done. [12]

Euvolemic Hyponatremia

Glucocorticoid deficiency

Low levels of ACTH caused by pituitary dysfunction leads to deficient hormone secretion by the adrenals resulting in this condition. Glucocorticoid deficiency diminishes water excretion due to non-osmotic AVP secretion. Maintenance of adequate aldosterone levels prevents renal sodium loss acting synergistically to prevent decrease in ECF levels. [12]

Hypothyroidism

Hypothyroidism causes changes in renal perfusion and glomerular filtration rate (GFR) secondary to systemic effects of thyroid hormone deficiency on cardiac output and peripheral vascular resistance. Plasma AVP levels become elevated when the hypothyroidism becomes severe and the effective arterial blood volume reduces enough to stimulate AVP secretion. Serum ADH levels are elevated in patients with cardiac dysfunction due to severe myxedema. [12]

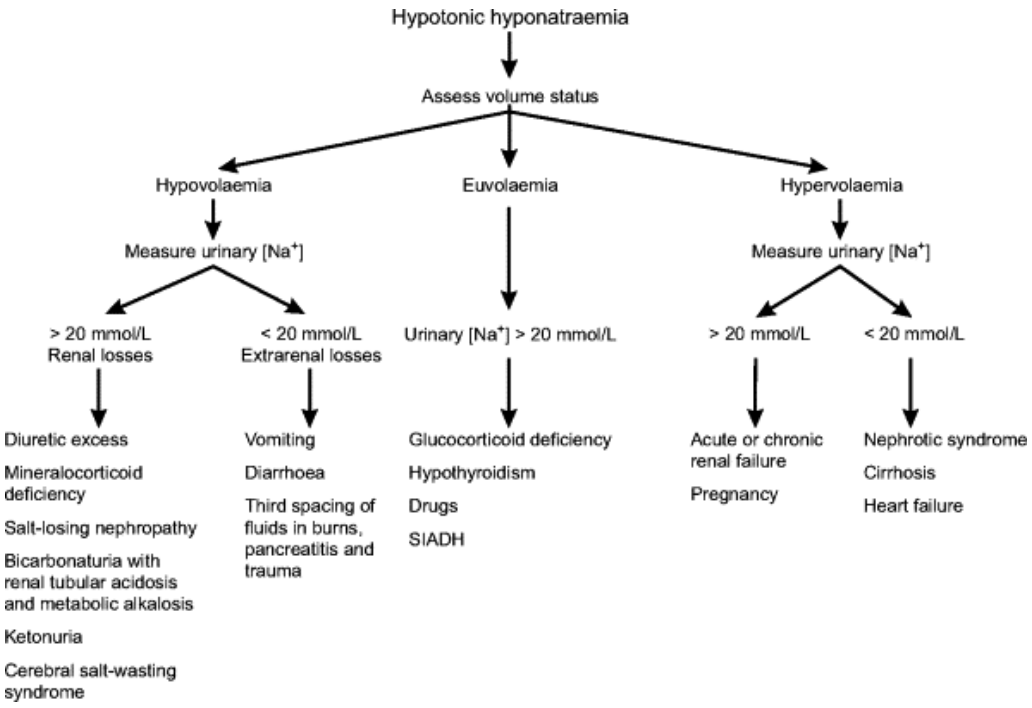
Decreased solute consumption

Patients consuming large quantities of beer with minimal food intake, and those on very low protein diet tend to develop euvolemic hyponatremia. The hyponatremia in these patients is neither dilutional nor depletional. [12]

Primary polydypsia

Many patients with acute psychosis secondary to schizophrenia, sarcoidosis or brain tumours tend to have impaired excretion of solute free water. Excess intake of water by these patients tends to produce hyponatremia.[12]

Figure 1: An algorithm for the differential diagnosis of hyponatremia based on assessment of volume status and measurement of urine spot sodium has been shown below[13]



Syndrome of Inappropriate Anti Diuretic Hormone secretion(SIADH)

This condition is an electrolyte imbalance in which low levels of serum sodium is caused by impaired urinary dilution due to an inappropriately elevated level of ADH. These patients are characterized by the absence of any osmotic imbalance or renal dysfunction.[14]

Table 3: Causes of the Syndrome of Inappropriate Antidiuretic Hormone (SIADH)[15]

Mechanism	Etiology
Increased secretion of ADH	Central nervous system: stroke, hemorrhage, infection, trauma, psychosis Drugs (most common): cyclophosphamide, vincristine, vinblastine, amiodarone, ciprofloxacin, theophylline, antipsychotic drugs (haloperidol, thioridazine, thiothixene), TCAs, MAOIs, bromocriptine, carbamazepine, clofibrate Pulmonary conditions: pneumonia, tuberculosis, acute respiratory failure, asthma, atelectasis Postoperative states: major abdominal or thoracic surgeries
Ectopic secretion of ADH	Lung cancers, tumors of duodenum and pancreas, olfactory neuroblastoma, malignant histiocytosis, mesothelioma, occult tumors
Increased sensitivity to ADH	NSAIDs, cyclophosphamide, tolbutamide, carbamazepine, mizoribine, chlorpropamide
Miscellaneous	Exogenous administration of vasopressin, desmopressin Cachexia, malnutrition, AIDS

ADH = antidiuretic hormone; MAOIs = monoamine oxidase inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Diagnostic Criteria (European Hyponatremia Network) [13]

Essential diagnostic criteria for SIADH[13]

• Decreased measured serum osmolality (<275 mOsm/kg H2O)

• Urinary osmolality >100 mOsm/kg H2O during hypo-osmolality

• Clinical Euvolemia

- No clinical signs of contraction of extracellular fluid (e.g., no orthostasis (a), tachycardia, decreased skin turgor or dry mucous membranes)

- No clinical signs of expansion of extracellular fluid (e.g., no edema or ascites)

• Urinary [Na+] >40 mmol/L with normal dietary sodium intake (b)

• Normal thyroid and adrenal function determined by both clinical and laboratory assessment

• No use of diuretic agents within the week prior to evaluation

Supporting diagnostic criteria for SIADH[13]

• Serum uric acid <4 mg/dL (<0.24 mmol/L)

• Blood urea nitrogen <10 mg/dL (<3.57 mmol/L)

• Fractional sodium excretion >1%; fractional urea excretion >55% (c)

• Failure to improve or worsening of hyponatremia after 0.9% saline infusion

• Improvement of hyponatremia with fluid restriction

a) Orthostatic changes in blood pressure and pulse rate are defined as a ≥20mmHg decrease in systolic blood pressure and/or ≥20bpm increase in the pulse rate upon going from the supine to standing position.[13]

b) Although high urine sodium excretion generally occurs in patients with SIADH, its presence does not confirm the diagnosis, nor does its absence rule out the diagnosis; urine [Na+] can also be high in patients with Addison's disease.[13]

Conversely, some patients with SIADH can have low urinary [Na+] if they become hypovolemic or solute depleted, which are conditions sometimes produced by imposed sodium and water restriction.[13]

c) Fractional sodium excretion = (urinary sodium excretion/serum sodium)/(urinary creatinine/serum creatinine)×100;[13]

Fractional urea excretion = (urinary urea/serum urea)/(urinary creatinine/serum creatinine)×100.[13]

Urine sodium excretion aids in distinguishing hypo-osmolality caused by a decreased effective arterial blood volume (in which case urine Na^+ is low due to renal conservation of Na^+) from dilutional disorders in which renal Na^+ excretion is normal or increased owing to ECF volume expansion. However, urine [Na^+] can also be high in renal causes of solute depletion such as diuretic use or Addison's disease. On the other hand, patients with SIADH can have low urine [Na^+] levels if they later develop hypovolemia or solute depletion. Therefore, although high urine [Na^+] excretion generally occurs in patients with SIADH, its presence does not confirm this diagnosis, nor does its absence rule out the diagnosis. [12]

Pathophysiology

Antidiuretic hormone (ADH) reduces the rate of urinary water loss. Therefore if a patient were to take surplus water, ADH would prevent excretion of the excess water. This would in turn increase the total body water further diluting the available sodium and causing hyponatremia. The amount of water required to do this would also depend of the quantity of free water excreted. In patients suffering from psychogenic polydypsia, a mild impairment of solute excretion would be enough to retain body water and dilute serum sodium. On the other hand, patients with high urinary concentration are constantly high require only a small amount of water intake to produce a similar imbalance.[14]

There are 2 mechanisms of by which an increase in body water such as that which occurs in SIADH causes hyponatremia. The first is by dilution where the serum sodium decreases in a manner proportionate to the elevation in total body water. The other mechanism is a net reduction in the sodium l available for exchange. Decrease in aldosterone secretion and elevated atrial natriuretic peptide levels cause natriuresis. In some patients vomiting induced by the hyponatremia itself tends to worsen the hyponatremia .[14]

Types of defective Urinary Water Excretion

Gary .L. Robertson[14] identified 4 types of inappropriate urine excretion. In 3 of these types, the osmoregulation of plasma AVP is abnormal because neither the hormone nor the urine concentration is fully suppressed as they should be when plasma sodium falls below the normal range.

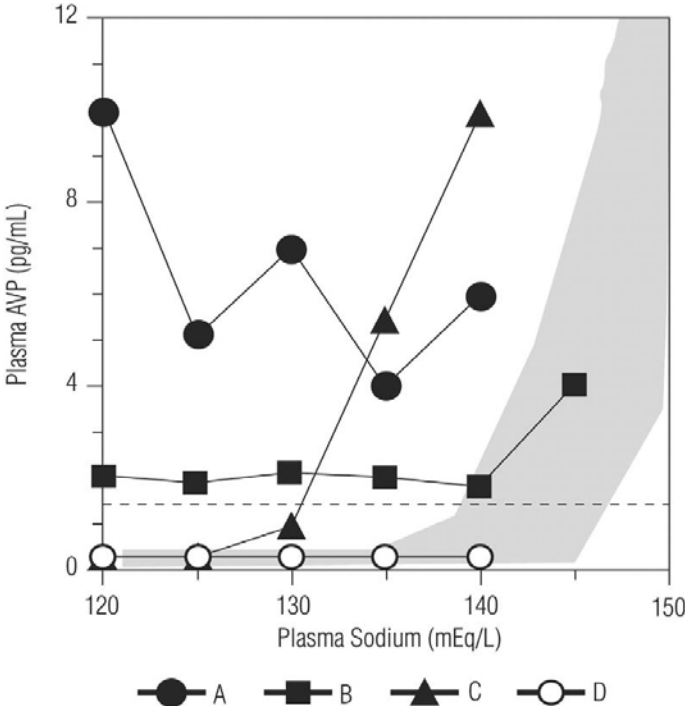


Figure 2: 4 types of ADH secretion in patients with SIADH. 1 mEq/L = 1 mmol/L.[14]

Type A: This pattern occurs in about 30% of SIADH and is characterized by an erratic, unregulated release of AVP in a level above that which produces maximum restriction of urination. Thus, changes in urinary concentration are minimal and the urine osmolarity remains fixed at the highest level (urine concentrating capacity is impaired in SIADH).[14]

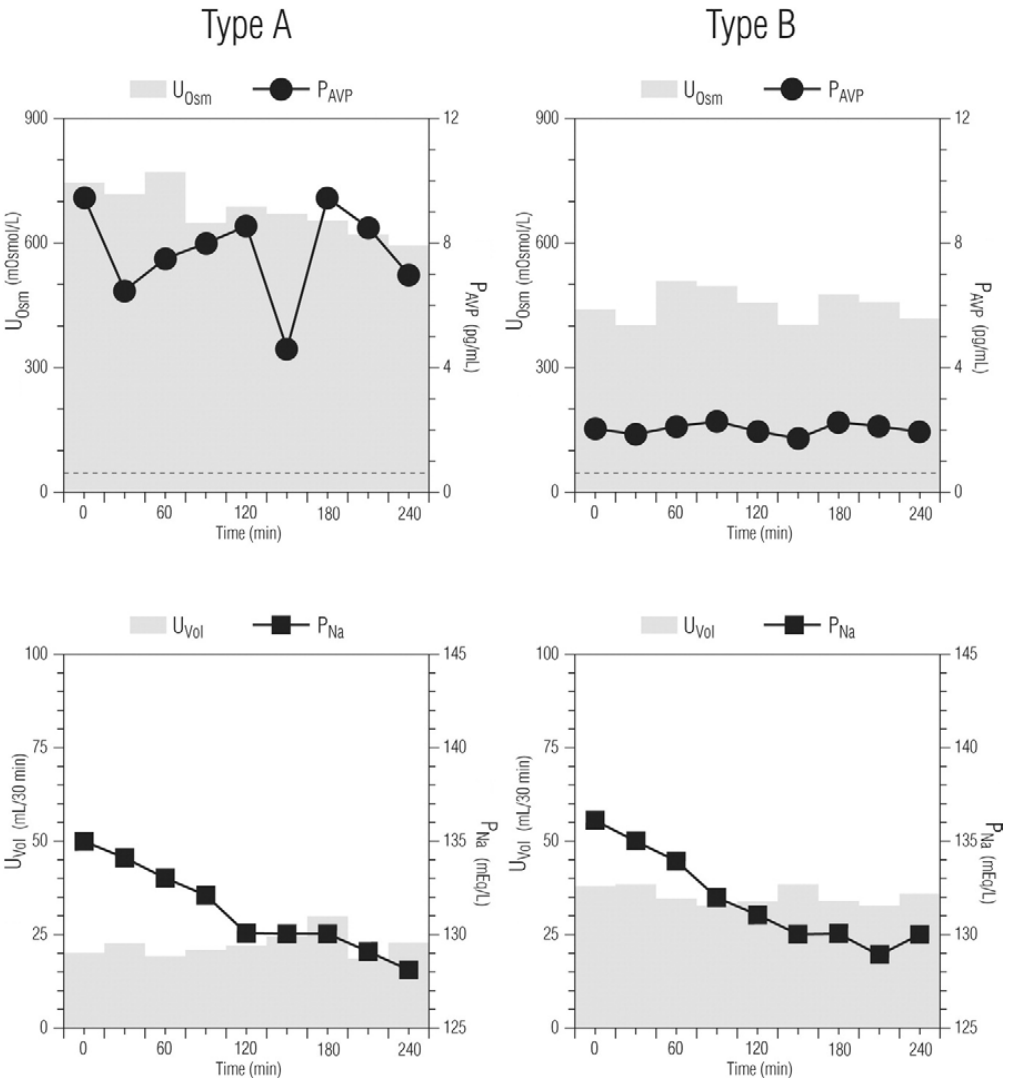
Type B: This pattern occurs in another 30% of SIADH. Here an insult to the posterior pituitary gland or damage to the factors inhibiting ADH secretion cause a small constant release of ADH which rises to appropriate levels once serum osmolality and serum sodium are within normal limits. Urinary concentration levels are fixed at a range below that in type A (Figure 2).[14]

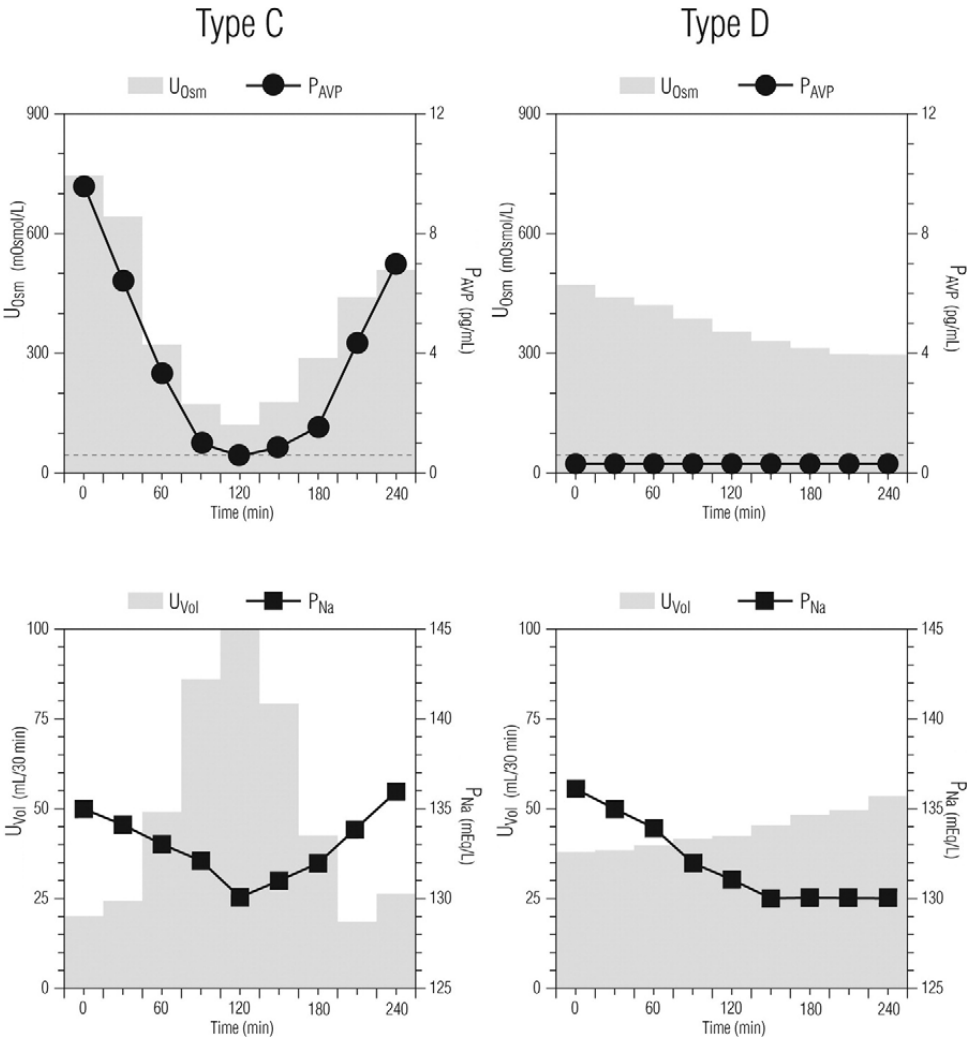
Type C: (Figure 2) This pattern also occurs in about 30% of SIADH. Here an insult to the peripheral mechanisms which control ADH secretion via baroreceptors causes a downward resetting of the entire osmoregulatory system. Patients with this disorder have low ADH levels when hyponatremic but inappropriately high levels when the plasma osmolarity and sodium levels start correcting and much before the hyponatremia is corrected.[14]

Type D (Figure 2): There is no aberration in the regulation of ADH (Figure 1). The exact cause of this defect is unknown. Mechanisms postulated include activation of the V2 receptor of ADH by genetic mutation, existence of an antidiuretic factor other than ADH or aberrant transportation of aquaporin 2 water channels mediating water reabsorption. These patients do not have any demonstrable ADH in serum under hyponatremic conditions and have normal cortisol levels. They fail to dilute their urine even when given an oral water load (Figure 2). [14]

There is no connection between the cause of SIADH and the type of osmoregulatory defect. [14]

Figure 3: Effect of an oral water load on AVP, urine osmolarity (UOsm) (expressed as milliosmoles per liter), urine flow (urine volume [UVol] in milliliters per 30 minutes), and plasma (serum) sodium (PNa) in patients with osmoregulatory defect types A, B, C, and D. 1 mEq/L = 1 mmol/L [14].





Management of SIADH [12]

Patients with SIADH who present with acute symptomatic hyponatremia are best treated with hypertonic (3%) saline given as a continuous infusion as they may not respond adequately to isotonic saline. Volume overload can be treated with intravenous furosemide, especially in patients with known cardiovascular disease. Correction is stopped when either: (1) patient becomes asymptomatic; or (2) a total correction of 18 mmol/L is achieved. Serum sodium is verified at regular periods to ensure the rate of correction. Serum sodium need not be normalized immediately but rather brought to a level of safety. Some patients excrete water to spontaneously rectify their hyponatremia.

Measured correction of chronic hyponatremia to < 10 - 12 mmol/L in 24 hours and to < 18 mmol/L in 48 hours ensures a slow reuptake of organic osmolytes by the brain. This helps in preventing osmotic demyelination syndrome. This syndrome is more common in the malnourished, alcoholics and those with severe liver disease. In high-risk patients, treatment should be aimed to stay beneath limits that have been laid out in patients without these risk factors. Severe demyelinating brain lesions rarely occur when the rate of correction > 25 mmol/L in 48 hours (based on patients with autopsy-proven myelinolysis).

In patients with acute hyponatremia such as those with water intoxication, the risk of developing osmotic demyelination with treatment is low. However, patients with chronic hyponatremia such as those with who have stopped treatment with desmopressin, those with cortisol deficiency, etc are at risk of developing this syndrome and hence their therapy should be controlled to limit the rate of correction of serum sodium using the end points mentioned above.

Patients with reset osmostat syndrome generally do not require treatment as the hyponatremia of such patients only varies around their reset level of serum sodium. Fluid restriction is the management of choice for SIADH. There should be no restriction of sodium in diet. Fluid restriction should include all kinds of fluids and requires to be continued for many days before correction of hyponatremia. The quantity of fluid restriction required depends on urine output plus insensible fluid loss (nonfood, fluids should be limited to 500 mL/day below the average daily urine volume);

Patients with chronic SIADH due to continuous loss of sodium from the urine require a high salt intake unless otherwise contraindicated. Failure of significant fluid restriction after several days of confirmed negative fluid balance should raise the possibility of other causes, including solute depletion and clinically unapparent hypovolemia.

When fluid restriction is started, drugs known to cause SIADH should be stopped. Pharmacologic intervention is reserved for refractory cases.

Demeclocycline is the agent of choice in SIADH. The drug causes a diuresis decreasing urine concentration even in the presence of high serum ADH levels. The dose of this drug ranges between 600 to 1,200 mg/day in divided doses. The drug takes many days to achieve maximal diuretic effects. Side effects include reversible azotemia and renal toxicity. Renal function should be monitored regularly in patients treated with demeclocycline and the medication should be discontinued if increasing azotemia is noted.

Other medicines described include lithium and urea which however have not found favor due to inconsistent results and significant side effects and toxicities.

Other drugs that decrease AVP hyper secretion (e.g., diphenylhydantoin, opiates, ethanol), are erratic and unpredictable. An exception is the κ-opioid receptors agonists, which are more specific for inhibition of AVP hyper secretion in animal studies and in clinical trials have successfully produced diuresis in patients with cirrhosis.

Vasopressin Receptor Antagonists [16]

By binding to the V2 receptor of the principal cell of the collecting duct, VRAs inhibit the renal action of arginine vasopressin, thereby stimulating water excretion and increasing serum Na^+. Drugs that block the action of AVP V2R selectively facilitate water excretion while sparing the solutes, and are therefore called aquaretic, as against diuretics which cause both water and solute excretion.

Conivaptan, a drug that blocks the mixed V1a/V2 receptor (V1a/V2RA), and tolvaptan, which selectively blocks the V2 receptor (V2RA), have recently been approved for treatment of hyponatremia with mild-to moderate symptomatology. Other V2RAs include satavaptan and lixivaptan.

Several randomized controlled trials have examined the efficacy and safety of VRAs in treating hyponatremia. VRAs are effective at raising serum Na^+ and effective water clearance in hyponatremia during the first 5 days of study. Short-term efficacy was greater in Euvolemic hyponatremia and high-dose VRAs. Meaningful increases in serum Na^+ occur by day 1 of VRA administration, practically without fluid restriction.

Cerebral Salt Wasting Syndrome

Cerebral salt wasting was identified in the 1950s when studies described the presence of polyuria, elevated urinary sodium levels, and dehydration despite the presence of a low serum sodium concentration and adequate fluid intake.

The exact frequency of CSW is not clear. This issue has been studied most rigorously in patients with aneurysmal SAH. In one study by Wijdicks EF et al [17] up to 67% (six of nine) of patients with hyponatremia after rupture of an intracranial aneurysm had CSW as the etiology of low sodium levels and 75% (six of eight) of SAH cases in another study by Nelson et al [18] also had CSW. A study by Sherlock et al [6] however, found that only 6.5% (4 of 62) of patients who presented with spontaneous SAH and subsequent hyponatremia had CSW as the cause of abnormally low sodium levels in their unselected cohort. The discrepancy between reported prevalence rates is a result of differences in study population size and with how CSW and volume depletion are defined [19]. There is no universally accepted gold standard in defining extracellular volume status or the specific parameters that classify cerebral-induced salt wasting, leading to significant variability between studies in the definition of low intravascular volume. For example, some authors have measured central venous pressure (CVP), whereas others have used isotope-labeled albumin. This difference in method of volume assessment and inclusion criteria could result in varying frequencies of affected. An additional confounding variable underlying the variability of CSW frequency in the literature is the manner in which sodium depletion is defined. Single versus multiple day cumulative sodium balance measurements often yield significantly different results [19].

CSW has been associated with a host of other CNS diseases in addition to aneurysmal SAH. Vespa estimated that 5% to 10% of traumatic brain injury patients to have salt wasting [19]. CSW is also seen in infectious meningitis, transsphenoidal pituitary surgery and cerebral malignancies, such as primitive neuro ectodermal tumors with intra ventricular dissemination, carcinomatous meningitis, glioma, and primary CNS lymphoma.

Pathogenesis

Despite the clear association between the presence of CSW and severe neurologic disease, the mechanism underlying this association has not been clearly identified.

Renin-Angiotensin-Aldosterone System

Renin is a circulating enzyme produced and stored within the kidney and released in response to low systemic and renal arterial perfusion. This hormone initiates a series of enzymatic steps involving the well known angiotensin-converting enzyme, resulting in the formation of angiotensin II (AT II).

Renin increases the sympathetic tone and stimulates the release of ADH. In the process it causes peripheral vasoconstriction and raises the blood pressure. The renal blood flow is thus increased and an appropriate rate of glomerular filtration and the percentage of sodium to be filtered are thus maintained. Aldosterone which is released in the process regulates extracellular fluid volume and serum potassium concentration thereby maintaining serum sodium homeostasis. RAAS activity is increased during periods of low circulating fluid volume and decreased when total circulating volume is sufficient or elevated. Neuronal synthesis of ATII takes place within the paraventricular nucleus and is released in the rostral ventrolateral medulla, a critical structure in the autonomic neural control of circulation. This implies a cerebrally mediated mechanism for influencing RAAS system exists. Tonic excitation of the rostral ventrolateral medulla influenced by endogenous AT II has been postulated to result in increased peripheral sympathetic tone. [19]

Sympathetic Nervous System Hypothesis

The autonomic nervous system increases the sympathetic tone during periods of intravascular depletion causing the secretion of renin from the kidneys. This stimulates the RAAS causing sodium and water retention. AT II by way of a positive feedback mechanism regulates the sympathetic nervous system activity by binding to specific receptors located within the subfornical organ (SFO) and area postrema. The SFO has direct projections to the paraventricular nucleus which are thought to control the activity of the rostral ventrolateral medulla causing an increase in the activity of the sympathetic nervous system by their projections to preganglionic sympathetic neurons within the intermediolateral cell column of the spinal cord. [19]

However, it has yet to be demonstrated that the changes in the interactions between the autonomic nervous system and the kidneys that are needed to produce a salt wasting state actually occur in the setting of acute cerebral injury. [19]

Natriuretic Peptide Theory

In the 1980s after it was discovered that atrial myocardial extracts induced a potent natriuretic response when infused into rats. These were called Natriuretic peptides. Contemporary studies looking into the origin of sodium and extracellular volume dysfunction in patients with SAH led to the realization that a natriuretic factor may be involved. A number of natriuretic substances have been discovered. These molecules defend against periods of excess water and salt retention by inhibiting the RAAS system, stimulating vascular relaxation, stopping both the excess sympathetic outflow and the generation of vasoconstrictor peptides. Four main natriuretic peptides with supposed associations with CSW have been identified: (a) atrial natriuretic peptide (ANP); (b) brain-natriuretic peptide (BNP); (c) C-type natriuretic peptide (CNP) (d) dendroaspis natriuretic peptide (DNP). The first three of these peptides are present within the CNS and have a tissue-specific site of production: ANP and DNP originate from the myocardial atria; BNP from the ventricles of the heart and CNP from the telencephalon, hypothalamus, and endothelium. [19]

The natriuretic peptides reduce the vascular sympathetic tone thereby dilating the smooth muscles of the the arteries and veins and leading to an increase in the glomerular filtration rate. These molecules also impair angiotensin mediated sodium reabsorption and resist the action of vasopressin at the collecting ducts. Natriuretic peptides produced locally within the adrenal medulla have inhibitory effects on mineralocorticoid synthesis causing low levels of aldosterone in the presence of hypovolemia.[19]

Several studies have shown elevated serum BNP after subarachnoid hemorrhage. McGirt et al [20] showed a time bound association between elevated BNP levels and hyponatremia in patients with SAH as well as presence of cerebral vasospasm. Besides BNP, other members within this peptide family, ANP in particular, have also been suspected to contribute to the development of CSW. Lately DNP, has also been implicated as a causative agent of hyponatremia in cases of aneurysmal SAH. More research would be required to work out more clearly the mechanism of action of each natriuretic peptide. [19]

Other theories

Kojima et al suggested that a mechanism other than one involving ANP, BNP, or ADH may be responsible for CSW based on their experiments on rats where rats with CSW were found to have levels of ANP decreased, while the BNP and ADH concentrations were unchanged. They concluded that a new, undetermined mechanism or one that involves DNP, likely underlies the etiology of CSW. [19]

Adrenomedullin (AM) a recently discovered endogenous peptide has also been proposed as a mediator of CSW. AM is a potent vasodilator with natriuretic and diuretic properties and elevation of serum levels of this peptide occurs immediately after SAH. The release of this hormone in aneurysmal SAH might serve a protective role against the development or worsening of cerebral vasospasm through its vasoactive properties. The site of CNS production of AM within the hypothalamus extends neuronal projections to regions within the brainstem and spinal cord, which can decrease sympathetic tone.[19]

Although new molecules and mechanisms have been described, BNP and ANP continue to be implicated as the main offenders toward the development of CSW, of which the former continues to be of primary suspect.

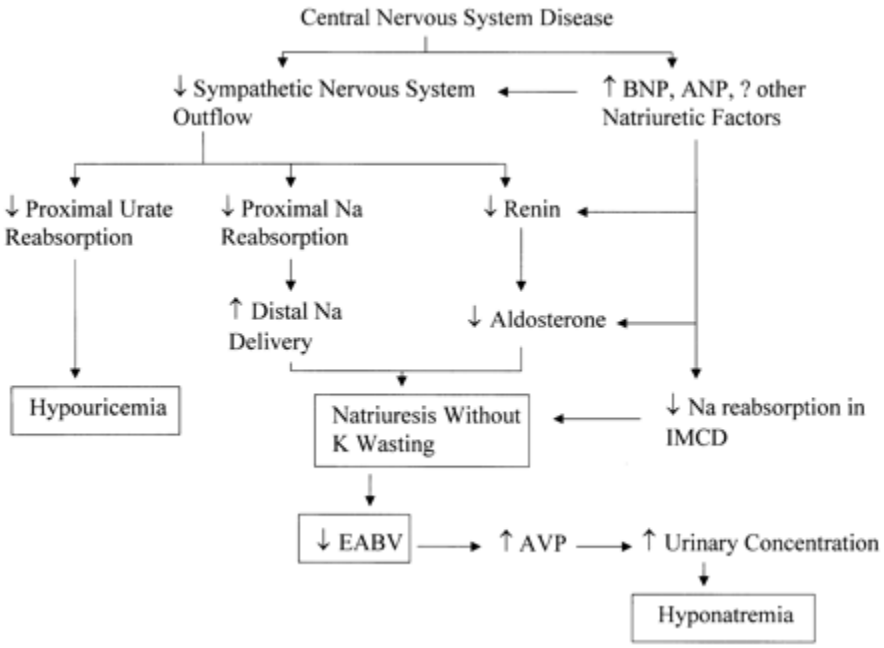


Figure 4: A proposed mechanism for the pathogenesis of cerebral salt wasting. IMCD, inner medullary collecting duct; EABV, effective arterial blood volume; AVP, arginine vasopressin; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide [21]

Management of Hypovolemic Hyponatremia[12]

The first step in the management of hypovolemic hyponatremia is the establishment of hyponatremia. One need to only correct the volume deficit thereafter and the sodium would correct subsequently. In patients who are dehydrated and also hyponatremic, correction of volume deficit would often have been started even before the results of blood tests have been obtained.

Fluid resuscitation should be pursued until the blood pressure normalizes. A diagnostic cum therapeutic challenge with isotonic saline when the volume status and/or diagnosis are ambiguous. Hypovolemic hyponatremia most often, except in cerebral salt wasting and thiazide induced diuresis, is chronic. Treatment of such cases therefore does not include the use of hypertonic saline. If 3% saline is to be used care must be taken to start the diuretic only after the patient is euvolemic.

Previous studies from our department had attempted to draw out a treatment strategy for hyponatremia with natriuresis based on blood volume status and hematocrit. Sivakumar et al[22] studied 21 patients and 3 control patients. Patients with hyponatremia were divided into 3 groups based on hematocrit, central venous pressure, and total blood volume. Group A which consisted of 16 patients who had hypovolemia and anemia. Group B patients included 5 patients with only hypovolemia. There were no patients in Group C which was for patients with hypervolemic. Patients in Groups A and B were treated with salt and isotonic fluid supplementation. An additional 500 ml of whole blood was given to patients in Group A. Hyponatremia was corrected in all the patients within 72 hours. The authors concluded that CSW was the most common cause of hyponatremia with natriuresis as most cases of hyponatremia are associated with hypovolemia.

Thereafter Damaraju et al.[1] tried to validate the protocol developed by Sivakumar et al[22] using central venous pressure as the sole measure of volume status of patients with hyponatremia and natriuresis. 26 cases were recruited into their study. Central venous pressure was used to classify patients as hypovolemic (<5 cm of water), normovolemic (6-10 cm of water), or hypervolemic (>11 cm of water). Hypovolemic patients were given fluids and salt. Euvolemic patients were given 12 g of salt per day in addition to normal fluids. Patients with anemia were transfused whole blood. They concluded that hyponatremia with natriuresis could be managed with guidance of volume status as determined by the central venous pressure and that the syndrome of hyponatremia with natriuresis was most often caused by CSW.

Serum Anti Diuretic Hormone (ADH):

ADH is a nanopeptide which is also referred to as Arginine Vasopressin (AVP). Neurons of the supraoptic and paraventricular nuclei produce ADH, transport them through the pituitary stalk and store them in the capillary plexus of the neurohypophysis. These plexuses drain into the systemic circulation through the cavernous sinus and the superior vena cava. [23]

The primary function of AVP is to decrease urine output. ADH binds to V2 receptors to increase the production of C-AMP which in turn increases the permeability of the luminal surface of the collecting duct through the expression of water channels called aquaporin 2. These water channels transport water back into the renal medulla increasing the urine concentration and reducing the urine output. [23]

Specialized osmoreceptors present near the supraoptic nucleus mediated the osmoregulation of ADH. They are sensitive to minute changes in plasma osmolality as small as 1%. When the serum osmolality reduces, ADH secretion is suppressed thereby permitting maximum water excretion through the urine. Even a minute increase in serum osmolality causes ADH levels to increase dramatically to maximally inhibit water excretion thereby keeping serum osmolality and sodium within the normal range 275 - 295 mOsm/kg. The sensitivity of the ADH response to osmotic stimulation varies widely.

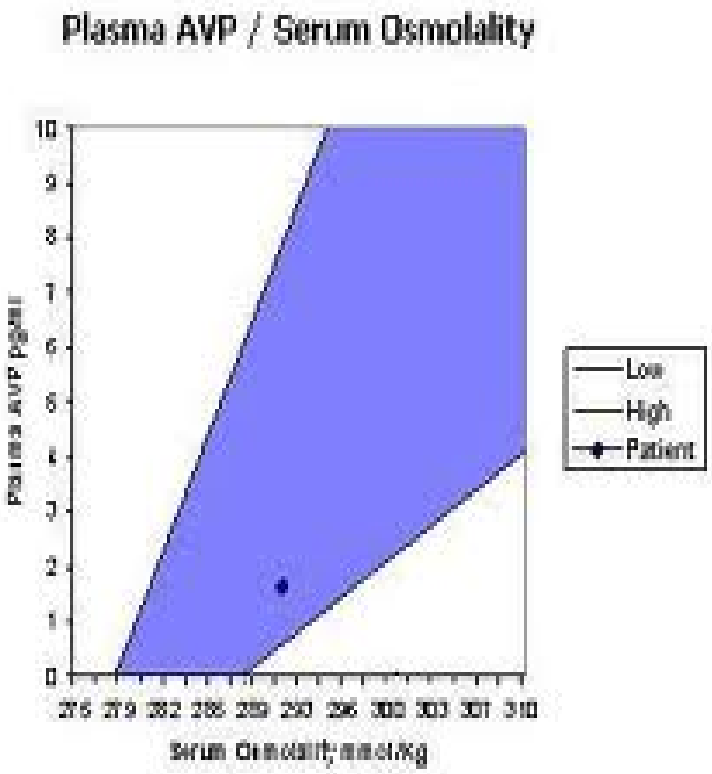


Figure 5: The relationship of plasma ADH to plasma osmolality in healthy adults [23]

Reduction in blood volume or arterial pressure of more than 10% to 20% can cause release of ADH. Other stimuli for ADH include nausea and vasovagal reactions. Emotional stress per se does not cause ADH release unless it also induces a vasovagal reaction. [23]

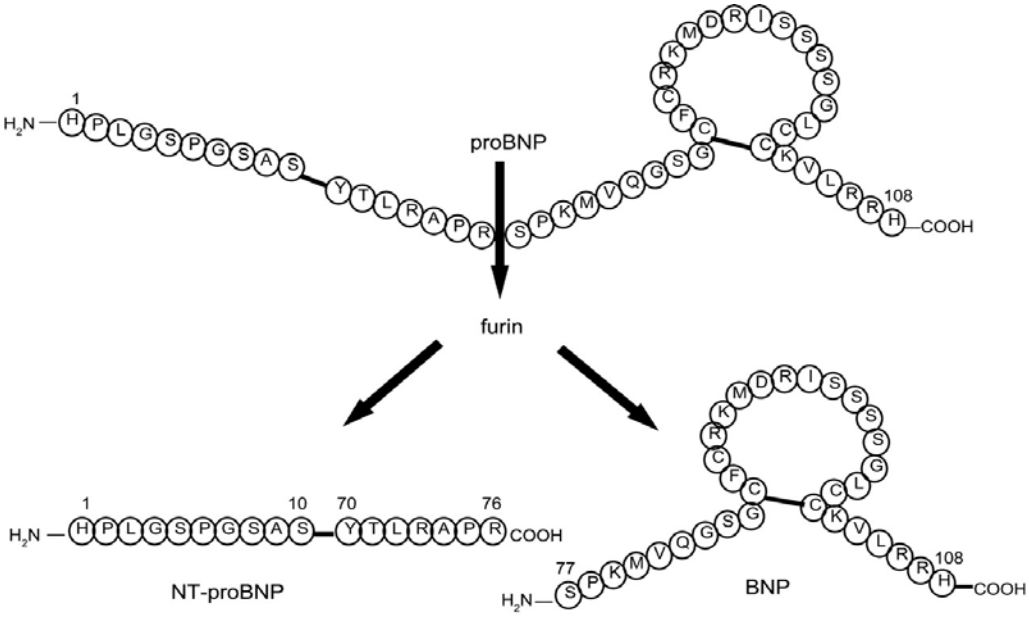
Inappropriate secretion of ADH is the main pathophysiology in SIADH. The main stimulus for the release of ADH from the supraoptic and paraventricular hypothalamic nuclei is hypernatremia of the blood perfusing the anterior hypothalamus. It can also be released in response to hypovolemia or hypotension even if the plasma is hypotonic. However in SIADH the ADH secretion is not suppressed by either hypotonia or normotensive normovolemia [24,25]. This ADH secretion causes water retention by the kidneys, increased the total body water and extracellular fluid volume, suppresses the renin-angiotensin-aldosterone mechanism and releases natriuretic substances.

Serum NT pro-BNP (N-terminal pro b-type natriuretic peptide):

The natriuretic peptides are a family of molecules consisting of several structurally-related hormones. At present, the natriuretic peptide family includes atrial natriuretic peptide (ANP), B-type (or brain) natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP) [26]

B-type natriuretic peptides are produced initially as a 134 amino acid pre-pro-peptide and cleaved into proBNP108, a precursor molecule which is stored in the secretory granules in myocytes. Upon release, proBNP108 is cleaved by a protease known as furin into N-terminal (NT)-proBNP (a 76 amino acid biologically-inert portion), and BNP (which is biologically active). In humans, NT-proBNP and BNP are found in largest concentration in the left ventricular (LV) myocardium, but are also detectable in atrial tissue as well as in the myocardium of the right ventricle. [26]

Figure 6: Schematic drawing of proBNP showing enzymatic cleavage into biologically active BNP and NT-proBNP. Hall C Eur J Heart Fail 2004;6:257-260 [27]



BNP is a cardiac hormone with natriuretic, vasorelaxant, aldosterone inhibitor and sympathetic outflow inhibiting properties.[19,28] It has been implicated in the development of CSW by inhibiting angiotensin induced sodium reabsorption at the proximal convoluted tubule and opposing the action of vasopressin at the collecting ducts. It also inhibits the synthesis of mineralocorticoids. [19] In addition to being found in the atria of the heart and stored in the cardiac ventricles, it is also stored in the hypothalamus. [29]

Although BNP and NTproBNP are derivatives of the same basic compound, they have certain differences which are significant in the clinical setting. BNP is circulated in the bloodstream as a biologically active compound which means it also is actively cleared from the plasma by neutral endopeptidases and natriuretic peptide receptors. It has a short half life of less than 20 minutes. Also, BNP cannot be used as a reliable marker as its concentration drops invitro as time progresses. BNP activates the kallikrein system when collected in glass tubes and causes a drop in the serum value. NTproBNP on the other hand being a precursor is stable both in vivo and invitro. It has a long half life of up to 120 minutes and can be kept in glass tubes for more than 72 hours, thus posing a striking advantage as a serum marker for hyponatremia.[26] The NT-proBNP assay is more sensitive than the BNP assay. [26]

Serum Aldosterone:

Aldosterone is a mineralocorticoid that is produced in the adrenal gland and forms part of the renin angiotensin aldosterone system (RAAS) which plays a central role in maintaining whole body sodium and water homeostasis. Aldosterone and ATII work synchronously to effect reabsorption of sodium from the distal tubules. Aldosterone forms a complex with the mineralocorticoid receptor in the distal tubule which travels inward into the cell nucleus to induce gene transcription. This process produces certain proteins that facilitate sodium reabsorption by several mechanisms, which are listed below.

1) Increasing sodium-potassium ATPase protein and activity at basolateral membranes of distal nephron segments.

2) Increasing the activity of enzymes of the tricarboxylic acid cycle.

3) Increasing the production of ATP to be used as an energy source for the sodium-potassium ATPase pump.

4) Increasing the expression and activation of epithelial sodium channels, which enhances sodium entry into the cell.

5) Increasing the permeability of the apical membrane to potassium, which drives the ATPase pump.

Taken together, the activation of multiple sodium transport mechanisms leads to augmented sodium and water reabsorption by the kidney. [30] Aldosterone is inhibited by natriuretic peptides and its serum levels are decreased in CSW and normal or high in SIADH. [28,29,31] The normal range of serum aldosterone varies between 40-310 pg/ml in the upright posture and between 10-160 pg/ml in the recumbent posture.

Serum Uric acid:

Uric acid (UA) is the final product of purine degradation with xanthine oxidase. Approximately 70% of the UA is excreted through the kidneys and 30% of the UA is excreted through the gastrointestinal tract. Beck [32] proposed that the coexistence of hyponatremia and hypouricemia (defined as serum urate less than or equal to 4 mg per 100 ml) differentiated SIADH from most other causes of hyponatremia. Beck observed that in 16 out of 17 patients with SIADH the serum urate levels were in the hypouricemic range. Hypouricemia is due to high uric acid clearance rates that results from the decrease in tubular uric acid reabsorption at the proximal tubule which occurs in SIADH due to increased extracellular volumes which in turn increases the fractional excretion of urea. [33,34] Expansion of extracellular fluid volume increases and contraction of extracellular fluid volume decreases the clearance of urate. In SIADH, there is volume expansion associated with low uric acid. A comparable situation is observed whenever exaggerated amounts of free water are consumed. Serum uric acid values more than 5mg/100ml are seen in patients with hyponatremia associated with a decrease in extracellular volume. [33] High uric acid values are also seen in the elderly who have lower glomerular filtration rates. Values less than 4mg/100 ml have also been observed in hypocortisolism, diuretics, potomania, cirrhosis and renal salt wasting. [33] CSW has been associated with normal, high or sometimes unexpectedly low levels of uric acid that persist despite correction of the hyponatremia. [2,11,21,25,35,36]

MATERIALS AND METHODS

We conducted a prospective study in our institution between August 2011 and February 2014 on post-operative neurosurgical patients who developed hyponatremia and natriuresis. Hyponatremia in this study was defined as a serum sodium less than 130 mmol/L and natriuresis as a urine spot sodium more than 25meq/l.[2,37]

Volume status was described, on the basis of CVP, as hypovolemic (< 5 cm of water), normovolemic (6-10 cm of water), and hypervolemic (> 13 cm of water).[1] The CVP was measured through a catheter that was passed through the antecubital, femoral or subclavian veins. Anemia was defined by a hematocrit of less than or equal to 27%. Normal hematocrit was equal to 28 to 48%.[2]

We included all non trauma postoperative neurosurgical patients who developed hyponatremia and excluded postoperative neurosurgical patients who were on diuretics, osmotically active agents (e.g. Mannitol) or had hypocortisolism or congestive cardiac failure.

76 patients of the 2950 postoperative patients who underwent neurosurgery in one Neurosurgical unit of the department developed hyponatremia. Of these 31 met the inclusion criteria and were recruited into the study while 45 patients with hyponatremia were excluded. Urine spot sodium was sent for all patients with hyponatremia to check for natriuresis. Packed cell volume (PCV), serum cortisol, plasma and urine osmolality was sent for all patients with hyponatremia and natriuresis. Patients with anemia would undergo blood transfusion or receive medications to correct their hyponatremia. Patients without anemia had a central line inserted and blood samples were sent for antidiuretic hormone (ADH), aldosterone, NT pro-BNP and uric acid. Serial serum sodium measurements were recorded. The total intake of fluids and output were measured. The study was divided into 2 phases.

Phase 1

In the first phase of the study we explored the feasibility of using serum markers to differentiate SIADH from CSW as a cause for hyponatremia with natriuresis. For this, we used central venous pressure, as this had been previously validated by our department in earlier studies. Once the differentiation was done based on the CVP, hypovolemic patients were treated with fluid resuscitation and oral salt supplementation while patients who were either euvolemic or hypervolemic underwent fluid restriction with oral salt supplementation. Hypertonic saline was reserved for patients who were symptomatic for hyponatremia such as those who presented with seizures or altered sensorium. These patients were monitored on a regular basis with serial measurements of serum sodium and a strict intake output chart. This was continued till patients attained a serum sodium of 130 mEq/L.

While inserting the central line we also took blood samples for antidiuretic hormone (ADH), aldosterone, NT pro-BNP and uric acid. The final diagnosis of SIADH or CSW was made based on the volume of fluid taken by the patient everyday during the duration of his illness. An intake of less than 2 liters over a period of 24 hours was considered as fluid restriction. The values of antidiuretic hormone (ADH), aldosterone, NT pro-BNP and uric acid were now compared with the final diagnosis. The normal value of NT pro-BNP in adults is less than or equal to 125 pg/ml. Hence, we chose this value as a cut off to differentiate between SIADH and CSW.

Phase 2

In Phase-2 we used this cut-off value of NT proBNP to treat 21 patients as SIADH or CSW until the serum Na^+ normalized. Patients with SIADH were managed with fluid restriction and sodium replacement. Patients with CSW were managed with appropriate IV fluids + oral salt. The sodium deficit was calculated using the following formula: 0.6 (weight in Kg) x (desired sodium – actual sodium); 0.5 for women

Hyponatremia was corrected at the rate of 10 – 12 mEq/l in the first 24 hours and < 18 mEq/l in the first 48 hours. Hypertonic saline was given in cases of patients symptomatic for hyponatremia or those with a sodium less than 120 mEq/L. The primary outcome of the study was correction of hyponatremia (serum sodium values of > 130 mEq/L

RESULTS AND ANALYSIS

A total of 31 patients were recruited into the study. They included 18(58%) males and 13(42%) females. The ages varied from 28-71 years with a median age of 46 years.

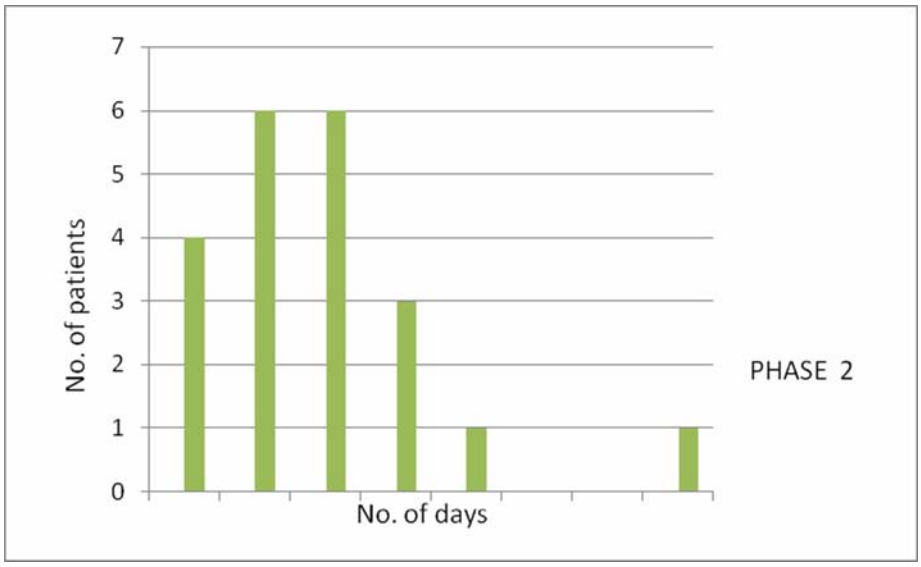
Table 4: The underlying diagnosis in these patients is as follows:

Pituitary adenoma	11
Glioma	5
Suprasellar cysts	3
Vestibular Schwannoma	2
Tuberculous meningitis with hydrocephalus	2
Colloid cyst	1
Tuberculum sella meningioma	1
Planum sphenoidale meningioma	1
Craniopharyngioma	1
Aneurysm	1
Lymphoma	1
Intramedullary tumor	1
Cervicomedullary Hemangioblastoma	1

Hyponatremia was corrected in all the patients.

In Phase 2 where the management was based on NT pro-BNP, the mean time duration to correct hyponatremia was 2.8 ± 1.63 days with a range of 1-8 days.

Figure 7: Time taken for correction of hyponatremia in patients in Phase 2



NT pro-BNP

Phase 1

Table 5: Patients in Phase 1 with their diagnosis, age, sex, CVP, NT pro-BNP, Aldosterone, Uric acid, type of fluid management and outcome

S.no	Diagnosis	Sex	Age	CVP	NTproBNP	Ald	Uric acid	Fluid restricted	Sodium corrected
1	Atypical pit. adenoma	M	30	8	54.8	84	2.7	Y	Y
2	TBM with hydrocephalus	F	35	3	222.7	50	1	N	Y
3	R frontal lymphoma	F	60	7	96.1	80	2.2	Y	Y
4	3rd ventricular colloid cyst	M	40	7	42.49	56	3.1	N	Y
5	Atypical choroid PLX papilloma	F	35	0	1053	874	4.3	N	Y
6	GH secreting pit adenoma	F	30	9	49.98	15	1.8	Y	Y
7	Tuberculum sellae meningioma	F	44	12	403.5	9.2	3.1	N	Y
8	TBM with hydrocephalus	F	48	0	1210	25	1.9	N	Y
9	Post-op L vestibular schwannoma	M	66	7	348.8	18	2	Y	Y
10	Suprasellar epithelial cyst	F	49	4	292.8	21.8	2.1	N	Y

2 patients (serial nos. 4, 7) with high CVP did not comply with fluid restriction. Their sodium however improved with their fluid intake and hence were considered as having CSW. One patient (serial no. 7) had a high CVP and NT pro BNP and improved with fluid restriction.

The first 10 patients were categorized into SIADH and CSW on the basis of their initial CVP. Of the 4 patients with a CVP less than 5 cm all had a concordant NT pro-BNP more than 125 pg/ml. However, of the 6 patients with a CVP more than 5 cm, 4 had an NT pro-BNP less than or equal to 125 pg/ml while the other 2 had a discordant NT pro-BNP more than 125 pg/ml. This is depicted in the table below:

Table 6: Correlation of NT proBNP values with CVP

NT proBNP	CSW (CVP < 5 cm)	SIADH (CVP > 5 cm)
NTproBNP(> 125pg/ml)	4	2
NTproBNP(≤ 125 pg/ml)	0	4

The above table gives NT proBNP a sensitivity of 100% and a specificity of 66.7% in detecting hypovolemia based on central venous pressure. The p value based on Fisher exact test was 0.07. The positive predictive value for predicting hypovolemia is 66.7% and the negative predictive value is 100%.

Table 7: In this table we have looked at the patients from the point of view of whether their serum sodium improved with fluid resuscitation or fluid restriction. The NT proBNP values in these patients have been correlated to their fluid intake. Based on this we get the following table

Of the 6 patients whose hyponatremia responded to fluid resuscitation 5 patients had an NT pro-BNP more than 125 pg/ml as expected while one patient had an NT pro-BNP less than 125 pg/ml. Similarly, of the 4 patients whose hyponatremia responded to fluid restriction 3 patients had an NT pro-BNP less than 125 pg/ml as expected while one patient had an NT pro-BNP more than 125 pg/ml. This can be seen in the following table

NT proBNP	Pts who responded to fluid resuscitation	Pts who responded to fluid restriction
NTproBNP(> 125pg/ml)	5	1
NTproBNP(≤ 125 pg/ml)	1	3

The above table gives NT proBNP a sensitivity of 83.3% and specificity of 75% to detect CSW based on the cut off value of 125 pg/ml. The positive predictive value of NT proBNP for predicting CSW is 83.3% and the negative predictive value is 75%. The p value based on Fisher exact test was 0.191.

Phase 2

Based on these results we proceeded to manage the remaining patients on the basis of their NT proBNP values alone. Patients with NT proBNP ≤ 125 pg/ml were treated as SIADH and those with NT proBNP > 125 pg/ml were treated as CSW. The results obtained were as follows.

9 of the 10 patients who required fluid resuscitation had an NT pro-BNP more than 125 pg/ml while all 11 patients whose hyponatremia corrected with fluid restriction has an NT pro-BNP less than 125 pg/ml.

Table 8: Correlation of management based on NT proBNP values with the final diagnosis of either SIADH or CSW in Phase 2

NT proBNP	CSW (Correction of hyponatremia with fluid resuscitation)	SIADH (Correction of hyponatremia with fluid restriction)
NTproBNP (> 125pg/ml)	9	0
NTproBNP (≤ 125 pg/ml)	1	11

This gave us a sensitivity of 90 % and a specificity of 100% for NT proBNP to detect CSW. The positive predictive value to predict CSW was 100% and the negative predictive value was 91.67%. The p value based on Fisher exact test was < 0.001.

Table 9: Combining the results of the 31 patients based on their fluid intake we get the following cumulative result (phase 1+2)

NT proBNP	CSW	SIADH
NTproBNP (> 125pg/ml)	14	1
NTproBNP (≤ 125 pg/ml)	2	14

NT proBNP had an overall sensitivity 87.50% of and a specificity of 93.33% to detect CSW. The positive predictive value to detect CSW was 93.33% and the negative predictive value is 87.50 %. The p value based on Fisher exact test was < 0.001.

Serum Aldosterone

All our patients had their blood samples taken in the recumbent position.

Patients with SIADH in our study had a serum aldosterone which ranged between 3.8 to 229 pg/ml with a mean of 54.33± 58.47 pg/ml.

Patients with CSW had an aldosterone between 9.2 to 874 pg/ml with a mean of 98.75 ± 225.28 pg/ml.

Uric Acid

The normal range of uric acid varies between 3-6 mg/dl in females and between 4-7 mg/dl in males.

Female patients with SIADH had their uric acid range between 1.4-3.8 mg/dl with a mean of 2.1 ± 0.86 mg/dl. Male patients with SIADH had their uric acid range between 1.2-6.3 mg/dl with a mean of 3.3 ± 1.59 mg/dl

Female patients with CSW had their uric acid range between 1-4.3 mg/dl with a mean of 2.3 ± 1.1 mg/dl

Male patients with CSW had their uric acid range between 2-6.3 mg/dl with a mean of 3.44 ± 1.3 mg/dl.

ADH

The normal serum range for ADH is up to 13 pmol/l. The ADH assay kit did not perform well and the ADH assay had to be abandoned during the study.

Urine Spot Sodium

In patients with SIADH the urine spot sodium ranged between 54-229 mmol/l with a mean of 118 ± 46.94 mmol/l

In patients with CSW the urine spot sodium ranged between 42-233 mmol/l with a mean of 129.18 ± 60 mmol/l.

We found that the values of serum aldosterone, uric acid and ADH coincided in patients with SIADH and CSW and hence these markers did not give us a tool that could be used to differentiate between SIADH and CSW.

DISCUSSION

Neurosurgery patients develop hyponatremia in the setting of natriuresis.[2] Hyponatremia with natriuresis is caused by either the syndrome of inappropriate anti diuretic hormone (SIADH) or cerebral salt wasting (CSW). [2] Opinion on how common SIADH and CSW are varies. Some authors argue that the existence of CSW is overstated. [38] These authors noted a connection between the rise in use of triple H therapy and CSW stating that large infusions of saline were causing pressure natriuresis and hence a negative balance of sodium along with a contracted extracellular fluid status which was being reported as CSW. Whereas others report that it is at least as common, if not more, than SIADH.[18,22] A recent study by Sherlock et al [6] on 116 patients with hyponatremia showed SIADH in 62%, CSW in 4.8% and diuretic induced hypovolemic hyponatremia in 26.7%. In our study, of the 31 patients having hyponatremia with natriuresis, we found SIADH in 15 (48.38%) and CSW in 16 (51.61%). The overall prevalence of postoperative hyponatremia with natriuresis in postoperative patients undergoing neurosurgery in our study was 1.05%.

The differentiation between SIADH and CSW has been difficult due to overlapping clinical and biochemical features and hence, it is based on the extracellular fluid status of the patients with SIADH being euvolemic or slightly hypervolemic and CSW being hypovolemic. [11] There remains a significant delay in the diagnosis and management of hyponatremia which increases the morbidity and mortality of these patients.

The determination of fluid status has been done using physical signs such as hypotension and tachycardia, laboratory markers like hematocrit, or blood urea nitrogen concentrations or by invasive methods using either radioisotope based volume studies [22] or using a central line. [1] Chung et al [39] showed that clinical assessment correctly identified only 47 percent of hypovolemic patients and 48 percent of normovolemic patients out of the 58 patients included in the study.

Radioisotope studies are not routinely used and are often difficult to undertake. In a previous study done in our department, Damaraju et al [1] used CVP measurement to determine the course of treatment for patients with hyponatremia. In their study based on CVP, 19 of 25 patients attained normal serum sodium values within 72 hours, and an additional 3 responded within the next 36 hours (108 h after entry into the study). One patient who was discharged on request had normalized her serum sodium a week later. In our study based on NT proBNP 23 of the 31 patients normalized their serum sodium values within 72 hours, and an additional 5 responded within the next 24 hours.

However newer meta-analyses have cast doubts whether central venous lines accurately measure blood volume and fluid responsiveness. Marik et al[40] did a meta-analysis of 24 studies which included 803 patients. Pooled correlation coefficients vary from -1 to +1 where -1 is a negative correlation, 0 means there is no correlation between the variables and +1 means a perfect correlation between the variables. The pooled correlation coefficient between CVP and measured blood volume was 0.16 (95% confidence interval [CI], 0.03 to 0.28). [40] Overall, 56 ± 16% of the patients included in this review responded to a fluid challenge. [40] The pooled correlation coefficient between baseline CVP and change in stroke index/cardiac index was 0.18 (95% CI, 0.08 to 0.28). [40] The pooled correlation between change in CVP and change in stroke index/cardiac index was 0.11 (95% CI, 0.015 to 0.21). [40] The review thus demonstrated a very poor relationship between CVP and blood volume as well as the inability of CVP/change in CVP to predict the hemodynamic response to a fluid challenge. [40] They concluded that CVP should not be used to make clinical decisions regarding fluid management.

The laboratory markers mentioned previously are not routinely done in clinical practice. Thus, there is no way to accurately differentiate SIADH and CSW. [41] Hence there is a need to explore other serum markers towards this end. While a number of serum markers have been identified, there are very few studies which have used them to differentiate SIADH and CSW. We therefore chose to look at NT pro BNP, uric acid, aldosterone and ADH in an attempt to evolve a less invasive and reliable way to differentiate between SIADH and CSW.

NT pro-BNP

Several previous studies have shown a rise in serum BNP concentration after subarachnoid hemorrhage [19] which is a common cause of CSW. [25] All 10 patients of Berendes with subarachnoid hemorrhage and CSW had elevated levels of BNP. [28] He also found that the levels of BNP and urinary sodium had a linear correlation.

McGirt et al found that 10 (63%) of 16 patients who experienced a large (more than threefold) increase in BNP in their cohort of 40 patients with SAH developed hyponatremia. 6 (25%) of 24 patients experiencing a minimal (less than threefold) increase in admission serum BNP level also developed hyponatremia [20].

We chose to look at NT proBNP as a marker to differentiate SIADH from CSW based on the literature on increased levels of natriuretic peptides in patients with CSW. To our knowledge this is the first study to look at NT proBNP in hyponatremia and also the first attempt at using this molecule to differentiate SIADH from CSW. Previous studies had mainly looked at BNP in subarachnoid hemorrhage.

In the first part of our study we had used a central line to categorize our patients into hypovolemic, euvolemic and hypervolemic categories based on the study by Damaraju et. al[1]. In the study by Damaraju et al[1] there were 19 patients with hypovolemia who were treated with fluid resuscitation and salt intake and only 7 patients who were normovolemic. The normovolemic patients were treated with normal fluid intake (volume not defined in the study) and additional salt. There were no patients who were hypervolemic. Based on current literature[12] we believe that the normovolemic patients have SIADH and require fluid restriction for effective correction of sodium. As the fluid balance of the patients who were normovolemic in Damaraju's study is not known, it could be possible that these patients had a low intake of fluids that would be normal for them under their circumstance. If these normovolemic patients consume large quantities of water, their hyponatremia would be exacerbated.

Hence, we used a CVP cut off of 5 cm of water to differentiate between SIADH and CSW. NT proBNP based on a cut off of 125 pg/ml did not correlate in 2 patients with a CVP more than 5 cm. While one patient improved with fluid restriction confirming the CVP diagnosis of SIADH, the other patient improved with fluid resuscitation confirming the diagnosis of CSW based on NT proBNP.

We found that NT pro BNP values were ≤ 125 mEq/L (i.e. within the normal range) in patients with SIADH and > 125meq/L in patients with CSW. This was in line with what we had predicted for NT proBNP based on previous studies. We therefore, decided to use 125 mEq/L as the cut off for NT proBNP to differentiate between SIADH and CSW. We found that NT proBNP based on this cut off had a good correlation with both the results of CVP, and the diagnosis of SIADH/CSW on the basis of fluid management.

Overall, NT proBNP values did not correlate with the fluid management used in 3 patients. 2 patients with SIADH based on NT proBNP improved with fluid resuscitation showing them to be cases of CSW rather than SIADH while one patient with CSW based on NT proBNP improved with fluid restriction instead. Thus we had 2 patients with false negative values and one patient with a false positive value of NT proBNP. This gave NT proBNP based on a cut off of 125pg/ml a sensitivity 87.50% of and a specificity of 93.33% in differentiating between SIADH and CSW. This finding correlates well with the findings of previous authors who detected high levels of BNP in SAH. It is well known that SAH is a common cause for CSW.[19] Our study showed high values of NT proBNP in patients with CSW. NT proBNP was also found to correlate well hypovolemia indicating that it could be used as a less invasive marker of the hydration status in patients with hyponatremia. The mechanism by which BNP causes CSW is through increase in glomerular filtration rate, inhibition of sodium reabsorption, opposition of the action of vasopressin and inhibition of mineralocorticoid synthesis. [19]

The mechanisms by which a CNS abuse of any sort leads to increased levels of natriuretic peptides are still being theorized. Some of them include:

(1) Direct damage to cortical and sub cortical structures where BNP exists leads to its unintended release into the circulation.

(2) Production and release of natriuretic peptides from the hypothalamus in disease states, such as SAH, to serve a protective role against elevated intracranial pressure.

(3) Myocardial tissue has also been proposed to be a source of elevated natriuretic peptide levels in CSW. Surges in sympathetic outflow in acute CNS injury leads to catecholamine- induced myocardial ventricular strain, thereby causing release of BNP from the atrial myocardium.

(4) Hypervolemic therapy itself, which is frequently administered after SAH can lead to myocardial chamber stretch and release of these peptides. [19]

NT proBNP is thus a good marker to distinguish CSW from SIADH. This marker is easily obtained from a blood sample thus avoiding the need for any invasive monitoring. NT proBNP has been used by the cardiologists as a prognostic marker in cardiac failure and hence the test kits for NT proBNP are widely available and not costly. The results are generally available within one hour and hence can be used for a quick diagnosis of hyponatremia with natriuresis.

Our results with NT proBNP need to be tested over a larger population and thus this study was limited by its small sample size. Also this marker cannot be used in patients with cardiac failure as the NT proBNP levels in these patients would be high.

Serum Aldosterone

Fichman et al[42] studied 4 patients with SIADH and found normal levels of aldosterone. All 10 patients studied by Berendes[28] with subarachnoid hemorrhage and CSW had low levels of aldosterone. Low levels of aldosterone in CSW have also been shown by other authors. [43]

However, contrary to the available literature we found that serum aldosterone levels were inappropriately low in both SIADH and CSW. Patients with SIADH had a serum aldosterone with an average of 48.35 ± 55.82 pg/ml while those with CSW had an aldosterone with mean of 109.45 ± 242.9 pg/ml. While Brain natriuretic peptide is known to suppress aldosterone in CSW, the mechanism due to which low levels of

aldosterone could be found in SIADH needs to be worked out. Thus aldosterone was not useful in differentiating between SIADH and CSW. Our study showed that hyponatremia with natriuresis is associated with levels of aldosterone in the lower side of the normal range irrespective of the cause being SIADH or CSW indicating a possible role for addition of mineralocorticoids like Fludrocortisone in the management of both SIADH and CSW.

Uric Acid

Beck [32] proposed that the coexistence of hyponatremia and hypouricemia (defined as serum urate less than or equal to 4 mg per 100 ml) differentiated SIADH from most other causes of hyponatremia. Beck observed that in 16 out of 17 patients with SIADH the serum urate levels were in the hypouricemic range.

In our study we found that the serum uric acid levels overlapping in both patients with SIADH and CSW. Our study also showed that hyponatremia with natriuresis is associated with hypouricemia irrespective of the cause being either SIADH or CSW. Thus this assay is not a reliable marker of either volume status or in distinguishing between SIADH and CSW. This finding has been confirmed by investigators like Maesaka[36] who therefore tried to look at the rate of correction of hypouricemia and fractional excretion rates of urate following correction of SIADH and CSW rather than at hypouricemia itself.

Antidiuretic hormone (ADH)

Serum ADH levels are known to be inappropriately elevated in up to 90% of patients with SIADH.[33,44] However SIADH has also been documented in patients with no detectable ADH. [2] We wanted to evaluate this point in our study but this had to be abandoned because of the poor performance of the kit used for ADH assay.

With the development of sensitive vasopressin radioimmunoassays capable of detecting the small physiologic concentrations of ADH that circulate in plasma there was hope that measurement of plasma vasopressin levels might become the definitive test for diagnosing SIADH. This has not occurred for several reasons. First, although plasma vasopressin levels are elevated in most patients with this syndrome, the elevations generally remain within the normal physiologic range and are abnormal only in relation to plasma osmolality. Second, 10% to 20% of patients with SIADH do not have measurably elevated plasma vasopressin levels and are at the limits of detection by radioimmunoassay. Third, and perhaps most important, most disorders causing solute and volume depletion or decreased EABV are associated with elevations of plasma vasopressin secondary to nonosmotic hemodynamic stimuli. [45]

The main limitation of our study was the small sample size. This was due to the fact that hyponatremia with natriuresis due to SIADH or CSW in patients undergoing neurosurgery is not very common. A larger sample size would have enabled us to obtain a cut off value of NT pro-BNP with the highest predictive value.

CONCLUSION

1. NT Pro-BNP is a useful marker to differentiate SIADH from CSW. A cut off value of 125 pg/ml could differentiate SIADH from CSW with a sensitivity 88.23% of and a specificity of 92.85% with a positive predictive value to detect CSW of 93.33%.

We would like to recommend NT pro-BNP as a readily available, quick and reliable marker to differentiate between CSW and SIADH.

2. Serum Aldosterone values were found to be inappropriately low in patients with both CSW and SIADH. Fludrocortisone would be beneficial for treating patients with both these conditions.

3. Serum Uric acid levels do not help differentiating SIADH from CSW.

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APPENDIX I Table 1: The various assays, their methods of estimation, reference ranges and instruments used are given in the table below

ASSAY	TECHNIQUE	MEASURING RANGE	REF RANGE	INSTRUMENT
ALDOSTERONE	Radioimmunoassay, SIEMENS, USA, COAT-A-COUNT	16.0 - 1200.0 pg/ml	SERUM: 10-160 lying; 40-310 pg/ml standing	WALLAC 1470 GAMMA COUNTER, FINLAND
ADH	Radioimmunoassay, DIAsource, Belgium	0.5-60 pmol/L	PLASMA: up to 13 pmol/L	WALLAC 1470 GAMMA COUNTER, FINLAND
CORTISOL	Automated Chemiluminiscent immunoassay,	0.2 – 50.0 µg/dL	SERUM: 7-25 µg/dL (0800am)	SIEMENS BAYER CENTAUR XP, USA
NT-pro-BNP	Automated Chemiluminiscent Immunoassay	20-35,000 pg/ml	Up to 125 pg/ml (<75yrs); up to 450 pg/ml (>75yrs)	SIEMENS IMMULITE 2000XPi, USA
OSMOLALITY	Freezing point depression Osmometer	100 – 2500 mOsmol/kg	SERUM 2 mOsm/Kg. URINE 1400 mOsm/Kg	GONOTEC OSMOMETER, GERMANY
SODIUM	Ion selective electrode Automated Chemistry Analyzer	50 – 200 mmol/L	SERUM 135-145 m URINE: M 40-220 287 mmol/L	Roche, Modular P800, GERMANY
URIC ACID	colorimetric, enzymatic, end-uricase, peroxidase. Automated Chemistry Analyzer	0.5 – 20.0 mg/dL	SERUM: M mg/dL, F 3.0-6.0 mg	Roche, Modular P800, GERMANY

APPENDIX II

Master Table

SNO	Hospital Number	Sex	Diagnosis	CVP	Symptomatic	NT- proBNP	Aldosterone	Uric acid	ADH	Urine spot Na
1	001082F	M	Atypical pit. adenoma	8	N	54.8	84	2.7		159
2	997082D	F	TBM with hydrocephalus	3	Y	222.7	50	1	1.41	59
3	030479F	F	R frontal lymphoma	7	Y	96.1	80	2.2	< 0.5	98
4	009286F	M	3rd ventricular colloid cyst	7	N	42.49	56	3.1	0.55	35
5	607731B	F	Atypical choroid PLX papilloma	0	N	1053	874	4.3	4.5	205
6	099870F	F	GH secreting pit adenoma	9	N	49.98	15	1.8	< 0.5	166
7	814192D	F	Tuberculum sellae meningioma	12	N	403.5	9.2	3.1	< 0.5	116
8	092066F	F	TBM with hydrocephalus	0	Y	1210	25	1.9	7.32	116
9	993615D	M	Post-op L vestibular schwannoma	7	Y	348.8	18	2	< 0.5	229
10	138073F	F	Suprasellar epithelial cyst	4	Y	292.8	21.8	2.1	< 0.5	150
11	172765F	M	Gonadotroph Pit. Adenoma	12	N	71.79	26	4.4	< 0.5	93
12	175641F	F	Non Funct Pit Adenoma	12	N	96.58	3.8	3.8	< 0.5	73
13	115762F	M	Suprasellar Arach cyst, Meningitis	12	Y	104	4.6	3.9	< 0.5	155
14	874610D	M	GH secreting pit adenoma	10	Y	15.89	54.6	1.2	< 0.5	117
15	115489F	M	Post op L VS	4	Y	605	Hemolysed	2.5	< 0.5	79
16	155895F	M	Non Funct Pit Adenoma	10	Y	459.2	10	2	< 0.5	161
17	193625F	M	Non Funct Pit Adenoma	9	Y	76.52	88.3	3.5	< 0.5	54
18	067396F	M	Non Funct Pit Adenoma	8	N	121	< 10	2.3	< 0.5	62
19	271752F	F	R Insular Oligodendroglioma	12	Y	121.6	< 10	1.4	< 0.5	137
20	254226F	F	Planum Sphenoidale meningioma	2	Y	468.5	< 10	2.4	0.51	175
21	322286F	F	Oligodenroglioma	8	Y	191	26.5	1.4	< 0.5	119
22	260633F	M	Craniopharyngioma, Meningitis	5	N	207.7	117	3.5	5.43	233
23	331338F	M	R A1-A2 aneurysm	0	Y	183.3	49	3.7	< 0.5	110
24	319421F	F	Sellar arachnoid cyst	10	Y	26.1	83.4	1.6	< 0.5	137
25	385963F	M	Right temporal GBM	10	Y	334	54	6.3		96
26	670117C	M	Right frontal GBM	12	Y	7.75	81	2.6		144
27	861592B	M	Right frontal fungal mass		N	124.8	229	4.8		79
28	772672F	M	Pit adenoma		Y	133.7	75.5	2.1		216
29	473465F	M	Cervicomedullary hemangioblastoma		N	375.4	Not ready	3.9		42
30	724818f	M	GH secreting pit adenoma		Y	58.14	18.29	6.3		136
31	453160D	F	Pituitary adenoma		N	97	13.6	2		86

Master Table Contd.

SNO	HNUM	Post-op Na								D1	D2	D3	D4	D5	D6	D7	Final diag CVP	Final diag NT proBNP	Final diag fluid mngt
		D1	D2	D3	D4	D5	D6	D7	D8										
1	001082F	117/117	118/123	131/134	134/135					950/800	1385/1500	890/1150	1050/2780	1150/3310	850/2240		SIADH	SIADH	SIADH
2	997082D	126	133/135							3500/2000	3850/2800	4515/2550	2190/1990	2270/4500			CSW	CSW	CSW
3	030479F	126	128/127	128	130					2280/VB	1850/VB	975/VB					SIADH	SIADH	SIADH
4	009286F	127	129	130	131					2925/2300	2400/3200	2175/2260	1725/1880	3150/850			SIADH	SIADH	CSW
5	607731B	128	137	139						2250/4100	1350/1090						CSW	CSW	CSW
6	099870F	128	123/120	122/121	128/136	140				2100/1700	1750/2750	1500/1850	1150/1750				SIADH	SIADH	SIADH
7	814192D	124	126/123	125/129	136/130	136				2490/1600	2775/1450	6330/4680	2635/2650	3350/2350			SIADH	CSW	CSW
8	092066F	116	120/123	129	133					2440/1950	3200/3600	2835/2620					CSW	CSW	CSW
9	993615D	128	126	125	123	124	130	132		2400/2275	2855/1500	2020/1600	1785/1450	2375/1250	1800/1920	1670/2275	SIADH	CSW	SIADH
10	138073F	123	132	135/129	131/137					4700/1500	4400/850	4575/900	4775/4500	3075/2700			CSW	CSW	CSW
11	172765F	127/127	127/133	134	136					2280/3830	2050/1450	1600/2270						SIADH	SIADH

12	175641F	126/129	139							2425/2600	1900/1800	1950/1750	2000/2500	2150/2300				SIADH	SIADH
13	115762F	129	126/129	136						3725/2300	2050/1875	2375/1300	2425/2150	2700/2225	3175/2500			SIADH	CSW
14	874610D	118/119	122/127	136						2680/2880	1650/2050							SIADH	SIADH
15	115489F	126	128/130	136						3125/600vb	2935/675vb							CSW	CSW
16	155895F	112/111	115/121	128/128	131/135					1610/1525	3850/2000	4100/1900	4070/2900					CSW	CSW
17	193625F	116/113	116/125	124/130	132/133	135				2275/3700	1325/4000	680/800	1400/1560					SIADH	SIADH
18	067396F	121	132/131	135						2150/1500	2050/2100	2300/2570						SIADH	SIADH
19	271752F	128/126	128/128	131/129	131/132					1400/1220	830/830	1295/770	825/1170	890/1510	880/1530			SIADH	SIADH
20	254226F	129/136	139							4425/1900								CSW	CSW
21	322286F	122/123	126/124	131/130						1320/3150	2150/3100	1505/1200	1050/VD					CSW	CSW
22	260633F	125	122/136							2650/1750	4150/1800	2875/1350	3350/1600					CSW	CSW
23	331338F	122/121	126/127	126	130					3600/2600	5570/4550	4900/4500	4500/4400					CSW	CSW
24	319421F	124	121/125	133	128/133	132				1190/1550	845/300	1000/570	1000/1270	1000/1360				SIADH	SIADH
25	385963F	120	117/119	125/124	127/131	136/137				2754/650	3470/2120	2945/1900	2210//2250					CSW	CSW

26	670117C	128	134/127	135						700/VB	1200/1950	800/550						SIADH	SIADH
27	861592B	126/121	117/125	127/126	129	122	129/129	132/129	140	1850/1930	920/2450	1450/650	1300/900	1150/950	1200/1300	1100/1000		SIADH	SIADH
28	772672F	117	114/114	111/120	122/129	132/132				1975/1200	2550/2450	2400/2300	1950/1800	1900/1850				CSW	CSW
29	473465F	127	138							2350/1700								CSW	CSW
30	724818f	114/114	118/125	125/130	130/135					1150/2400	960/1500	2990/6950	700/900					SIADH	SIADH
31	453160D	127	127/127	131/135	138					3600/3900	875/3450	1100/690	1100/1300					SIADH	SIADH

APPENDIX III

PROFORMA FOR EVALUATION OF POSTOPERATIVE HYPONATREMIA AND NATRIURESIS

S.No:

Date:

Name:

Age:

Hospital No.:

Diagnosis: 1)

2)

3)

Date of Surgery: Previous Surgery:

Type of Surgery: Previous RT:

PREOPERATIVE HORMONAL PROFILE FOR PITUITARY PATIENTS

T4	8AM Cortisol
FTC	FSH
TSH	LH
Prolactin	Testosterone
HGH	IGF-1

Post-operative Sodium

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

Post-operative Cortisol day 1 day2 day3

Day of onset of hyponatremia: Day …. (after surgery)

CVP:

Symptomatic: Y /N

INVESTIGATIONS SENT:

Uric acid	Cortisol
BNP	Aldosterone
ADH	TFT

Urine spot Sodium

Time to normalize:

Treatment:

Medication	Dose		Day1	Day2	Day3
Hydrocortisone					
Fludrocortisone					
3% Saline	Y / N				
ICU required	Y / N				
Fluid restriction	Y / N				
Intake / Output					
Day	1	2	3	4	5	6	7