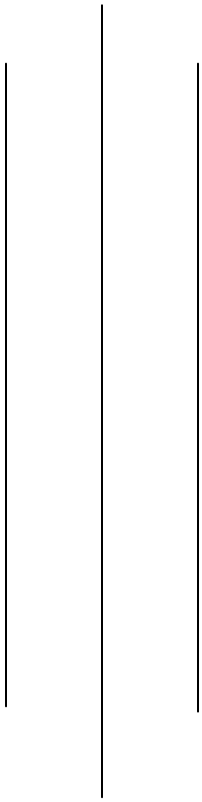
Hyponatremia in Patients with Traumatic Brain Injury: Etiology, Incidence and Severity Correlation



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Dr. Subash Lohani
Principal Investigator

Abbreviations

ACE	Angiotensin Converting Enzyme
ACTH	Adreno Cortico Trophic Hormone
ADH	Anti Diuretic Hormone
AH	Anterior Hypopituitarism
ANP	Atrial Natriuretic Peptide
ARB	Angiotensin Receptor Blockers
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CHF	Congestive Heart Failure
CNP	C-type Natriuretic Peptide
CNS	Central Nervous System
CSWS	Cerebral Salt Wasting Syndrome
CT	Computed Tomography
CVP	Central Venous Pressure
DI	Diabetes Insipidus
EABV	Effective Arterial Blood Volume
ECF	Extra Cellular Fluid
EFV	Extracellular Fluid Volume
FENa	Fractional Excretion of Sodium
FEUA	Fractional Excretion of Uric Acid
GCS	Glasgow Coma Scale
GFR	Glomerular Filtration Rate
GH	Growth Hormone
GI	Gastro-Intestinal
GOS	Glasgow Outome Scale
HCT	Hematocrit
HIV	Human Immunodeficiency Virus
HPA	Hypothalamo-Pituitary-Adrenal
IL	Interleukin

ICA	Internal Carotid Artery
MCA	Middle Cerebral Artery
mmol	milli moles
mosm	milli osmoles
MRI	Magnetic Resonance Imaging
NaCl	Sodium Chloride
ODS	Osmotic Demyelination Syndrome
OLC	Oubain-Like Compound
P_{Cr}	Plasma Creatinine
P_{Na}	Plasma sodium
P_{UA}	Plasma Uric Acid
PAI	Primary Adrenal Insufficiency
PCWP	Pulmonary Capillary Wedge Pressure
RTA	Renal Tubular Acidosis
SAH	SubArachnoid Hemorrhage
SIADH	Syndrome of Inappropriate Anti Diuretic Hormone
SNS	Sympathetic Nervous System
SSRI	Selective Serotonin Reuptake Inhibitor
T3	Tri-iodothyronine
T4	Thyroxine
TBI	Traumatic Brain Injury
TSH	Thyroid Stimulating Hormone
TURP	Trans-Urethral Resection of Prostate
U_{Cr}	Urinary Creatinine
U_{Na}	Urinary Sodium
U Na	Urinary Sodium Concentration
U_{UA}	Urinary Uric Acid
V2	Vasopressin receptor type 2

Contents

Prologue

Idea about this research was generated while going through hyponatremia in neurosurgical patients. There seemed to exist ample of studies in hyponatremia in patients with subarachnoid hemorrhage. The relative dearth of knowledge in that among trauma patients incited the research enthusiasm. Both of these are common neurosurgical population where this problem exists. Adding further intrigue, researchers seemed to be busy trying to find a new answer amidst Fractional Excretion of Uric Acid (FEUA) that would solve the riddle between the Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) and Cerebral Salt Wasting Syndrome (CSWS).

As research oriented investigations had to be done in hyponatremic patients, arrangement of grant was of utmost essence. The grant was finally accepted by NHRC, and the research commenced on April 2008.

After intensive literature review, expert opinions, grant approval, data collection, and analysis, we have come up with a report that justifies all those days of hardship. Though the initial expected population was not met by the research because of time constraints, we believe that we have been able to produce considerable results, which shall not only add to the existing information pool, but also enforce further research endeavors.

On days to come, large population based prospective research will be necessary to build up the findings of this study.

Executive Summary

Hyponatremia is common in neurosurgical population, prominently in patients with Sub-Arachnoid Hemorrhage (SAH) and Traumatic Brain Injury (TBI). Two common etiologies, namely the Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) and Cerebral Salt Wasting Syndrome (CSWS), are primarily responsible. Differentiation among two conditions is based on volume status of patient. Given a typical case scenario, distinction might not appear difficult. Yet, exceeding number of cases have a borderline picture with diagnostic confusion and impediment in therapeutic intervention. Researchers are thus making an attempt of differentiation based on biochemical alterations.

This is a prospectively designed study on hyponatremia in patients with TBI. All patients above 16 years with moderate to severe head injury and mild ones with intracranial lesion on CT scan were enrolled in the study. Over a period of 6 months, 40 patients fulfilled the criteria.

Serum sodium level was monitored daily till 14th day. Central Venous Pressure (CVP) measurement was done for the assessment of volume status. All patients with moderate or severe head injury and those who underwent surgical evacuation of lesion had routine CVP catheter insertion. In the remaining, CVP was inserted after detection of hyponatremia. Correct position of CVP catheter was confirmed in all the cases with post-procedure check x-ray; with contrast injection if necessary. Measurement of Fractional Excretion of Uric Acid (FEUA) was done in all cases at the detection of hyponatremia and after its correction.

Since volume depletion is hazardous in TBI patients, fluid restriction was not done even with a diagnosis that was consistent with SIADH. Oral salt supplementation and intravenous normal saline was the first line management in all hyponatremic patients. If

patients did not respond to this, then moderate fluid restriction (1500 ml/day) was done for SIADH and oral fludrocortisone was used for CSWS.

Out of 40 consecutive patients enrolled in the study, seven were excluded from the analysis for several reasons; early mortality, transfer to other centres or medical co-morbidities likely to produce hyponatremia. Of 33 patients that remained for analysis, nine (27.27%) developed hyponatremia.

Mean age of hyponatremic patients was 38.44 years with 55.6% patients of 17-30 age group, and male to female ratio of 3.5:1. Mild, moderate and severe head injury formed 36.36, 27.27 and 36.36% respectively. Hyponatremia occurred at the same incidence of 33.33% in both mild and moderate injuries, while in severe cases, the incidence was only 16.66%. Hyponatremia was seen in Rotterdam CT score two, three and four in increasing incidence of 22.2, 33.3 and 44.4% respectively (r 0.983, p value 0.017), while there was no significant correlation with initial GCS (p value 0.15).

All patients had some form of abnormality in CT scan. Frontal location was the most common site, both among total patients and hyponatremic patients, 63.6 and 66.7% respectively. Intraparenchymal lesion was the most common CT abnormality overall as well as in hyponatremic patients, 66.7 and 88.9% respectively. None of them had an intraventricular extension. There were eight (88.9%), three, two and one patients respectively with intraparenchymal lesion, epidural hematoma, pneumocephalus and traumatic SAH who developed hyponatremia; three had more than one type of lesion. All varieties of the lesions were associated with hyponatremia, but none of the four patients with subdural lesions showed hyponatremia. Right and left unilateral, and bilateral lesions were all associated with equal incidence of hyponatremia of 33.33%.

Based on volume status, among nine hyponatremic patients, five (55.5%) had SIADH, three (33.3%) had CSWS and remaining one had inconclusive picture. All patients, but

one, responded well to above mentioned first line treatment strategy. One patient required fludrocortisone in addition.

Six patients (66.6%) developed hyponatremia within first week of injury. Mean duration of hyponatremia was 1.78 days. In three patients it lasted for two days, while in two other, it lasted for three days. One patient had hyponatremia 113 mEq/L and the other down to 120 mEq/L. Rest of the patients had sodium levels above 125 mEq/L. Two patients had recurrence of hyponatremia, at 11^{th} and 12^{th} day, both of which were corrected within a day with first line treatment. Measurement of FEUA prior to and after correction of hyponatremia did not reveal consistent measurements as suggested in the literature.

Mean hospital stay was 26.73, 27.5 and 24.67 days among total, non-hyponatremic and hyponatremic patients. Similarly, mean Glasgow Outcome at discharge was 3, 2.92 and 3.22. There was no significant difference of means in duration of hospital stay or GOS at discharge.

Regarding the type, site and side of the lesion, Glasgow Coma Scale at the time of presentation, surgical intervention, individual CT characteristics, Rotterdam CT score, mean hospital stay and GOS at discharge, none of the variables were found to have significant association with the occurrence of hyponatremia.

Introduction

Traumatic brain injury (TBI) is a non-degenerative, non-congenital insult to the brain from an external mechanical force causing temporary or permanent neurological dysfunction, which may result in impairment of cognitive, physical and psychosocial functions.[1] TBI is preferred over the term head injury, which rather is a non-specific and antiquated term indicating clinically evident external injuries to the face, scalp and calvarium that may or may not be associated with TBI.[2]

Population-based studies in the United States suggest that the incidence of TBI is between 180 and 250 per 100,000 population per year. Males are uniformly at higher risk of TBI than are females, with M/F ratio ranging from 1.5:1 to 1.7:1. A trimodal age-specific TBI incidence has generally been reported with incidence peak noted in early childhood, late adolescence/early adulthood, and in the elderly. Automobile, motorcycle, and bicycle collisions were responsible for half of all TBIs, while one third resulted from falls, and rest from recreational injuries/sports(10%), firearms etc. The percentages of TBI severity are typically mild, 80%; moderate, 10%; and severe, 10%. Mortality varies by severity but is high in those with severe injury and in the elderly. TBI is estimated to be the primary cause of death in one third to one half of all traumatic deaths.[2]

Consequence of TBI ranges from neurological and cognitive impairment to personality, behavioral changes and lifestyle consequences.[3] From a clinical point of view, all endpoint consequences are a result of either primary or secondary brain injury. While primary brain injury is the result of direct mechanical damage that occurs at the time of trauma, secondary brain injury is the damage to neurons due to the systemic physiologic responses to the initial injury.[4] Since primary injury is irreversible, all possible efforts are needed to minimize the secondary brain injury.

Post traumatic endocrine complications pose a great challenge in the management of TBI. Early recognition of these subtle problems can produce a significant impact on the

progress and outcome. Approximately 30-50% of patients who survive post TBI demonstrate endocrine complications. SIADH is the most common TBI-associated neuroendocrinopathy causing hyponatremia. The incidence is reportedly as high as 33%. Relatively less common causes include anterior hypopituitarism (AH), cerebral salt wasting syndrome (CSWS), and primary adrenal insufficiency (PAI). Hypopituitarism could be in the form of hypothyroidism, adrenal insufficiency, hypogonadism, hyperprolactinemia, DI, and growth hormone (GH) deficiency. Both CSWS and PAI are peripheral causes of hyponatremia after a TBI, while SIADH, AH, and DI have central endocrine etiologies.[5]

Hyponatremia is a common electrolyte disorder in the setting of central nervous system (CNS) disease, including TBI.[6] Hyponatremia could be hypotonic, isotonic or hypertonic.[7,9] Clinical manifestations of hypotonic hyponatremia are largely related to dysfunction of the central nervous system as it causes entry of water into the brain, resulting in cerebral edema. It can develop acutely or insidiously, and the condition being asymptomatic if it develops over a stretch of time allowing the brain to adapt. Whereas patients with persistent asymptomatic hyponatremia require slow-paced management, those with symptomatic hyponatremia must receive rapid but controlled correction. Although morbidity varies widely in severity, serious complications can arise from the disorder itself as well as from errors in management.[7]

Hyponatremia has been shown to have an association with the severity of brain injury [6] and is clearly related to deterioration of the patient's condition and must therefore be treated properly. [8] In TBI, hyponatremia is often attributable to impaired free water excretion, SIADH or to excessive renal sodium excretion, CSWS and less often to hypopituitarism.[10,1] In a TBI rehabilitation setting, SIADH is the most common cause of hyponatremia. [5]

SIADH is characterized by hyponatremia in the setting of an inappropriately concentrated urine, increased urine Na^+ concentration and evidence of normal or slightly increased intravascular volume. The primary pathogenic mechanism underlying SIADH is

excessive ADH release causing renal water reabsorption and resulting in expansion of the ECF volume.[10] Posttraumatic SIADH is caused by uncontrolled release or constant non-suppressible leak of anti diuretic hormone (ADH) as a result of damage to the pituitary stalk or the posterior pituitary [11,6] or because of "resetting" of osmoreceptors to release ADH at lower serum osmolalities. [6]

CSWS is characterized by hyponatremia, clinical evidence of volume depletion and renal Na^+ wasting, without an obvious disturbance in the pituitary–adrenal axis in association with a CNS disease. Decreased sympathetic input to the kidneys, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), oubain like compound (OLC) etc, have been implicated in its pathophysiology. [10, 6]

The distinction between these two disorders is of considerable clinical importance given the divergent nature of the treatments. Owing to the considerable overlap of the laboratory findings, determination of extra cellular fluid (ECF) volume remains the primary means of distinguishing these disorders. ECF volume is increased/ normal in SIADH, whereas it is low in CSWS. [10] Consequently, fluid restriction is the treatment of choice in SIADH with occasional need for hypertonic saline, whereas the treatment of CSWS comprises vigorous Na^+ and volume replacement or occasionally fludrocortisone to prevent renal Na^+ wasting. [10, 6]

Statement of the problem and Rationale of the research topic

Hyponatremia in TBI is a complication of common occurrence and clearly has a deleterious effect in the outcome of the patient. Lack of clarity in the cause has often led to inappropriate management. Thus establishment of proper diagnosis is of utmost importance, and the confusion needs elucidation.

Hyponatremia in TBI is an under-researched topic, most of them being limited just as case reports. Most of the studies that have been done are retrospective, thus starkingly lacking necessary variables and unable to give composite conclusive results.

There exists a lot of controversy ranging from the non-existence of CSWS to it being more common than SIADH in neurological patients.

With these considerations at hand, the importance of a prospective research with above mentioned objective need not be over emphasized.

Literature review

Classification of traumatic brain injury (TBI) is necessary to accurately describe patient series and requires grouping of patients according to specific characteristics. In clinical practice, the clinical severity of TBI is generally classified as severe, moderate or mild according to the level of consciousness as measured with the Glasgow Coma Scale (GCS) [40]

Mild: GCS 14-15

Moderate: GCS 9-13

Severe: GCS 3-8

But the increased use of early sedation, intubation and ventilation in more severe patients has decreased the value of GCS for purposes of classification. [23] Alternatively, in more severe patients, TBI can be classified according to morphological criteria based on computed tomography (CT) or magnetic resonance imaging (MRI). Although MRI may be more sensitive for detecting small white matter lesions in a later phase after TBI, CT examination remains the investigation of choice in the acute phase. [23]

Various studies have confirmed the predictive value of the CT classification, and the international guidelines on prognosis include the CT classification as a major CT predictor based on Class I evidence. [23] The Marshall CT classification identifies six groups of TBI patients, based on morphological abnormalities on the CT scan. This classification is increasingly used as a predictor of outcome. [23] Maas et al. [23] performed a study comparing the predictive value of the Marshall CT classification with alternative CT models, concluding that it is preferable to use combinations of individual CT predictors rather than the Marshall CT classification alone for prognostic purposes in TBI, and thus came up with Rotterdam CT score.

Marshall CT Classification: [23]

CT grade	**Criteria**
diffuse injury I	No visible intracranial pathology seen on CT scan
diffuse injury II	Cisterns present with midline shift of 0-5 mm and/ or lesions densities present: no high or mixed density lesion > 25 cm3 may include bony fragments and foreign bodies
diffuse injury III(swelling)	Cisterns compressed or absent with midline shift of 0-5 mm, no high or mixed density lesion >25cm3
diffuse injury IV(shift)	Midline shift of >5 mm; no high or mixed density lesion >25cm3
evacuated mass lesion	Any lesion surgically evacuated
non-evacuated mass lesion	High or mixed density lesion >25 cm3, not surgically evacuated.

Rotterdam CT score: [23]

CT characteristics	**Category**	**Score**
Basal cistern	Normal	0
	Compressed	1
	Absent	2
Midline shift	No or ≤ 5mm	0
	>5 mm	1
Mass lesion	Epidural	0
	Non-epidural	1
IVH or tSAH	Absent	0
	Present	1
Sum score		+1*

* +1 is added to the sum score to make to make the grading numerically consistent with Marshall CT grading and motor score of GCS.

Glasgow outcome scale (GOS) is often employed in the outcome assessment following TBI. [39]

Glasgow Outcome Scale:[39]

Score	Meaning
5	Good recovery; resumption of normal life
4	Moderate disability; disabled but independent
3	Severe disability; conscious but disabled
2	Persistent vegetative state
1	Death

Hyponatremia

As mentioned earlier, hyponatremia, defined as serum sodium levels of <136 mEq/L,[6,5,7] is a common electrolyte disorder in the setting of CNS pathology, including traumatic brain injury, tumors, intracranial infections, and stroke.[6]

Severity of hyponatremia can be graded as:

- Mild: >120 mmol/ L
- Moderate: <120 mmol/ L, asymptomatic
- Severe: <120 mmol./ L, symptomatic

Depending on the duration, hyponatremia can be acute or chronic [12]

1. Symptomatic :
    - Acute: <48 hrs
    - Chronic: >48 hrs
2. Asymptomatic: almost always > 48 hrs

Pseudohyponatremia is a spurious form of iso-osmolar and isotonic hyponatremia associated with severe hypertriglyceridemia or paraproteinemia.[7] Drop in the level of sodium occurs by 1 mmol/L for every 4.6 gm/L of plasma lipids. [12]

Hyperglycemia is the most common cause of translocational hyponatremia. An increase of 100 mg per deciliter (5.6 mmol per liter) in the serum glucose concentration decreases serum sodium by approximately 1.7 mmol per liter, with the end result a rise in serum osmolality of approximately 2.0 mOsm/ kg of water. Retention of hypertonic mannitol, which occurs in patients with renal insufficiency, has the same effect. [7]

By far SIADH and CSWS are the ones that are frequently encountered in the setting of TBI. Causes of hyponatremia other than SIADH and CSWS to be considered in these patients include iatrogenic fluid overloading, medication induced diuresis, congestive heart failure, renal or liver disease, hypothyroidism, and adrenal insufficiency. Artifactual hyponatremia that can be seen with hyperglycemia and hypertiglyceridemia must also be taken into account. [6]

Various etiologies of hyponatremia can be classified based on the serum osmolality and EFV status.[9] The table is presented on the following page.

Clinical manifestations of hypotonic hyponatremia are largely related to dysfunction of the central nervous system. They are more conspicuous when the decrease in the serum sodium concentration is large or rapid (i.e., occurring within a period of hours). Headache, nausea, vomiting, muscle cramps, lethargy, restlessness, disorientation, and depressed reflexes can be observed. Whereas most patients with a serum sodium concentration exceeding 125 mmol /l are asymptomatic, those with lower values may have symptoms, especially if the disorder has developed rapidly. Complications of severe and rapidly evolving hyponatremia include seizures (lowers the seizure threshold[4]), coma, permanent brain damage, respiratory arrest, brain-stem herniation, and death. These complications often occur with excessive water retention in patients who are essentially

euvolemic (e.g., those recovering from surgery or those with primary polydipsia); menstruating women appear to be at particular risk. [7]

<table>
<tr><th colspan="4">Type of hyponatremia</th><th>Etiology</th></tr>
<tr><td colspan="4">Hypertonic</td><td>Hyperglycemia , Mannitol</td></tr>
<tr><td colspan="4">Isotonic</td><td>Hyperlipidemia(triglyceridemia), Hyperproteinemia(multiple myeloma)</td></tr>
<tr><td rowspan="5">Hypotonic (all of these conditions have raised ADH levels; while appropriate in rest, in SIADH it is inappropriate)</td><td rowspan="4">Impaired renal water excretion capacity</td><td colspan="2">High EFV</td><td>CHF, Cirrhosis, Nephrosis, Renal Failure(acute/chronic)[7], Pregnancy[7]</td></tr>
<tr><td colspan="2">Normal EFV</td><td>SIADH, Hypothyroidism, Adrenal insuffiency, Reset osmostat, , beer potamania[7], thiazide diuretcs*[7]</td></tr>
<tr><td rowspan="2">Low EFV</td><td>U Na >20 mEq/L</td><td>CSWS, Diuretics(thiazide, K sparing), ACE inhibitors, ARB, Hypoaldosteronism, IV RTA/ bicarbonateuria(RTA disequilibrium stage of vomiting)[7], Ketonuria[7], Osmotic diuresis(glucose, urea, mannitol)[7]</td></tr>
<tr><td>U Na <10 mEq/L</td><td>Bleeding, Vomiting, Diarrhea, Third space fluid sequestration(pancreatitis, peritonitis, bowel obstruction, muscle trauma, burns)[7], Excessive sweating[7]</td></tr>
<tr><td>Excessive water intake</td><td colspan="3">Primary polydipsia !, Sodium free irrigant solution(Post TURP syndrome, hysteroscopy, laparoscopy) !!, accidental ingestion of large volume of watetr(swimming), multiple tap water enema,</td></tr>
</table>

* Na/ K depletion, stimulation of thirst, and impaired urinary dilution are implicated

! Often mild water excretion defect also present

!! Hyponatremia is not always hypotonic

Pathophysiology

Hypotonic hyponatremia causes entry of water into the brain, resulting in cerebral edema. Because the surrounding cranium limits expansion of the brain, intracranial hypertension develops, with a risk of brain injury. Fortunately, solutes leave brain tissues within hours, thereby inducing water loss and ameliorating brain swelling. This process of adaptation by the brain accounts for the relatively asymptomatic nature of even severe hyponatremia if it develops slowly. Partial restoration of brain volume occurs within a few hours as a result of cellular loss of electrolytes (rapid adaptation). The normalization of brain volume is completed within several days through loss of organic osmolytes from brain cells (slow adaptation). [7]

These intracellular, osmotically active solutes contribute substantially to the osmolality of cell water and do not adversely affect cell functions when their concentration changes. The reuptake of organic osmolytes after correction of hyponatremia is slower than the loss of organic osmolytes during the adaptation to hyponatremia. [13]

Nevertheless, brain adaptation is also the source of the risk of osmotic demyelination. Although rare, osmotic demyelination is serious and can develop one to several days after aggressive treatment of hyponatremia by any method, including water restriction alone. [7] Areas of the brain that remain most depleted of organic osmolytes are the most severely injured by rapid correction. [13] Shrinkage of the brain triggers demyelination of pontine and extrapontine neurons that can cause neurologic dysfunction, including quadriplegia, pseudobulbar palsy, seizures, coma, and even death. Hepatic failure, potassium depletion, and malnutrition increase the risk of this complication. [7] The brain's reuptake of myoinositol, one of the most abundant osmolytes, occurs much more rapidly in a uremic environment, and patients with uremia are less susceptible to osmotic demyelination. [13]

SIADH and CSWS

The term, cerebral salt wasting, was introduced by Peters and colleagues in 1950. In a report of three patients, they described renal salt wasting in the setting of central nervous

system disease. Although this phenomenon was supported by other reports, it was eclipsed by the identification of SIADH in 1957. [6]

SIADH

ADH, [6] an octapeptide, is released from cells in the neurohypophysis in response to changes in serum osmolality. Changes of ≤ 2% can be sensed by osmoreceptors in the hypothalamus; increases in osmolality increase secretion of ADH, and decreases in osmolality suppress its secretion. ADH secretion is also altered in response to changes in intravascular volume. In the kidney, ADH increases the permeability of the terminal distal tubule and medullary collecting ducts to water via V2 receptor mediated insertion of aquaporin-2 in principle cells. [37] In SIADH, excessive levels of ADH occur as a result of disease- or drug-induced pituitary release of ADH or ectopic production of ADH. [6]

Etiology of SIADH: [7]

<table>
<tr><th>Malignancy</th><th>CNS disorder</th><th>Drugs</th></tr>
<tr><td>• Pulmonary tumors
• Mediastinal tumors
• Extrathoracic tumors</td><td>• Acute psychosis
• Mass lesions
• Inflammatory and demyelinating disease
• Stroke
• Hemorrhage
• Trauma</td><td rowspan="3">• Desmopressin
• Oxytocin
• PG synthesis inhibitors
• Nicotine
• Phenothiazines
• Anti- depressants (Tricyclics, SSRI)
• Opiate derivatives
• Chlorpropamide
• Clofibrate
• Carbamazepine
• Cyclophosphamide
• Vincristine</td></tr>
<tr><td>Pulmonary disorders</td><td>Miscallaneous</td></tr>
<tr><td>• Infection
• Acute respiratory failure
• Positive pressure ventilation</td><td>• Post operative states
• Pain
• Severe nausea
• HIV infection</td></tr>
</table>

Robertson [6] categorized SIADH according to patterns of ADH release. In his analysis, organic brain disease leads to excessive release of ADH by either "resetting" osmoreceptors to release ADH at lower serum osmolalities or causing a constant, non-suppressible "leak" of ADH from the hypothalamus, unrelated to serum osmolality, the latter of which might be the result of damage to the pituitary stalk or the posterior pituitary during TBI. [11]

To elucidate the relationship between interleukin-6 (IL-6) and SIADH as well as IL-6 and hypothalamo pituitary adrenal (HPA) axis activity, Gionis et al [14] studied eight previously healthy children, who after sustaining head trauma, presented SIADH during hospitalization. They concluded that IL-6 secreted during an aseptic inflammatory state, such as sustaining head trauma with SIADH, is quantitatively correlated to ADH, indicating that this cytokine is directly and/or indirectly involved in the pathogenesis of SIADH.

SIADH is a volume expanded state. The primary pathogenic mechanism underlying SIADH is ADH release causing renal water reabsorption and resulting in expansion of the ECF volume. In spite of a decreased serum Na^+ concentration, normal renal Na^+ handling is characteristic of SIADH. Expansion of ECF volume is not typically accompanied by overt signs of hypervolemia, such as edema or distended neck veins, because only one-third of retained water is distributed in the ECF space. [10]

Edema is not seen during SIADH, for unknown reasons. The absence of this important clinical clue to the presence of water retention can be a source of confusion in differentiating SIADH from CSWS and underscores the importance of evaluating volume status in patients suspected of having SIADH. [6]

The presence of high urinary sodium concentrations in SIADH is not fully understood. Natriuresis in SIADH may be caused by an increase in the glomerular filtration rate (GFR), a decrease in aldosterone secretion, or a decrease in renal tubular sodium reabsorption caused by other hormonal or direct neural effects. [6] Most likely explanation is that, GFR and renal plasma flow results in decreased proximal Na^+ reabsorption and

increased urinary Na^+ excretion which is equal to dietary Na^+ intake. [10] But this appearance of natriuresis during SIADH can be another source of confusion in differentiating SIADH from CSWS, in which renal sodium loss is the primary feature.[6] Substances such as uric acid and urea nitrogen, which are reabsorbed proximally in concert with Na^+, also tend to be reduced because of diminished proximal reabsorption. [10]
The traditional criteria[6] for the diagnosis of SIADH are:

1) low serum sodium (<135 mEq/L)
2) low serum osmolality (<280 mOsmol/L)
3) high urine sodium(>18 mEq/L)
   (variation in the cut off urinary sodiem levels: U Na > 25 mEq/L [10] or >20mEq/L [9, 21] or > 18mEq/L [6])
4) urine osmolality greater than serum osmolality
5) normal thyroid, adrenal, and renal function
6) absence of peripheral edema or dehydration

It should also be noted that in SIADH, urine osmolality may be less than serum osmolality but not as low as it should be because urine should be maximally diluted in the presence of severe hyponatremia.[15] The appropriate renal response to hypoosmolality is to excrete the maximum volume of dilute urine, i.e., urine osmolality and specific gravity of less than 100 mosmol/kg and 1.003, respectively.[36]

But, the diagnosis of SIADH cannot be made in the presence of severe pain, nausea, stress, or hypotension, factors that can stimulate ADH secretion even in the presence of serum hypotonicity. [6]

Additional methods for the diagnosis of SIADH include the water-load test and measurements of serum or urinary ADH. Although water-load test is considered to be definitive for SIADH, it is dangerous unless the serum sodium level exceeds 124 mEq per liter and the patient has no hyponatremic symptoms, and is difficult to perform in patients with acute intracranial disease. An alternative is to measure serum or urinary

levels of ADH. Whereas ADH is typically undetectable in hyponatremic states, it is often detectable and excessive regarding serum osmolality in SIADH. ADH levels must be cautiously interpreted, because ADH secretion is promoted by stress, pain, and increased intracranial pressure, which are common features of intracranial disease. [6]

CSWS

CSW is a volume-depleted state characterized by the evidence of negative salt balance and reductions in both plasma and total blood volume, caused by a centrally mediated excessive renal Na^+ excretion. The onset of this disorder is typically seen within the first ten days of an acute cerebral insult [10] and typically resolves within 3-5 days of the onset of hyponatraemia. [16]

CSWS has been described in patients with metastatic adenocarcinoma of the lung and carcinomatous meningitis, pituitary exploration and biopsy, parietal glioma, and transsphenoidal surgery for pituitary adenoma; in elderly patients after head injury; and in two pediatric patients with central nervous system disease (closed head trauma in one and seizure disorder, spastic diplegia, mental retardation, and hydrocephalus in the other). [6]
The mechanism by which cerebral disease leads to renal salt wasting is poorly understood. The most probable process involves: [10]

1. disruption of neural input into the kidney
2. central elaboration of a circulating natriuretic factor

By either or both mechanisms, increased urinary Na^+ excretion would lead to a decrease in effective arterial blood volume (EABV). A probable site for depressed renal Na^+ absorption in CSW is the proximal nephron. Because this segment normally reabsorbs the bulk of filtered Na^+, a small decrease in its efficiency would result in the delivery of large amounts of Na^+ to the distal nephron and, ultimately, into the final urine. [10]

Decreased sympathetic input to the kidney could be an explanation for impaired proximal reabsorption, because the sympathetic nervous system (SNS) has been shown to alter salt and water handling in this segment through various indirect and direct mechanisms.

Because the SNS also plays an important role in the control of renin release, decreased sympathetic tone could explain the failure of circulating renin and aldosterone levels to rise in patients with CSW. The failure of serum aldosterone levels to rise in response to a decreased EABV can account for the lack of renal K^+ wasting, despite a large increase in distal delivery of Na^+. In this regard, hypokalemia is not a feature of CSW. [10]

In addition to decreased neural input to the kidney, release of one or more natriuretic factors could also play a role in the renal salt wasting seen in CSWS. ANP and BNP have several effects that could lead to the clinical syndrome of CSWS. The ability of these compounds to increase GFR accounts for some of the natriuresis; however, even in the absence of a change in GFR, urinary Na^+ excretion increases because of a direct inhibitory effect on Na^+ transport in the inner medullary collecting duct. These peptides can also increase urinary Na^+ excretion without causing hypokalemia. For example, ANP and BNP are associated with decreased circulating levels of aldosterone because of direct inhibitory effects on renin release in the juxtaglomerular cells of the kidney and direct inhibitory effects on aldosterone release in the adrenal gland. In addition, inhibition of Na^+ reabsorption in the inner medullary collecting duct would not be expected to cause renal K^+ wasting, because this segment is distal to the predominant K^+ secretory site in the cortical collecting duct. As ECF volume becomes contracted, proximal Na^+ reabsorption would increase, resulting in less distal delivery of Na^+ to the collecting duct. Decreased Na^+ delivery protects against K^+ wasting in the setting of high circulating levels of aldosterone. ANP and BNP can also directly decrease autonomic outflow through effects at the level of the brain stem. In this manner, natriuretic peptides can act synergistically with CNS disease to decrease neural input to the kidney. [10]

Although atrial stretch is thought to be the principle mechanism for cardiac ANP release, intracranial disease may lead to a disturbance of the brain's control over ANP secretion. Levels of ANP alone do not account for the hyponatremia of CSWS. [6]

BNP is largely of cardiac ventricular origin. It is secreted by the cardiac ventricles in response to increased pressure or stretch of the ventricles and has biological effects similar to those of ANP. [6] But it is also found in brain. There is evidence that BNP might

be the more probable candidate to mediate renal salt wasting. It is not known whether either brain or cardiac tissue or both contribute to the increased BNP concentrations found in these patients. [10]

C-type natriuretic peptide (CNP) is present in the brain and cerebrospinal fluid in far greater amounts than ANP or BNP and is found in high concentrations in the vascular tree, especially in the endothelium but circulating levels of CNP are lower than those of ANP or BNP. In contrast to ANP and BNP, CNP seems to lack natriuretic activity and. seems to act as a venodilator via local or paracrine action.[6]

Brain OLC has a role in CSW but it is unlikely that circulating OLC is the blood-borne natriuretic factor that is hypothesized to mediate CSW. Other potential mediators like bradykinin, oxytocin, adrenocorticotropic hormone, α/β-melanocyte-stimulating hormone, parathyroid hormone, and calcitonin have all been experimentally shown to produce natriuresis. The role of these substances in CSWS and their association with intracranial disease remain to be investigated. [6]

A comparison of the anatomy of intracranial lesions with the occurrence of CSWS might be useful in identifying parts of the central nervous system involved in CSWS. Specific brain lesions are associated with natriuresis. CSWS has been documented in patients with tumors in the right posterior thalamus and the right parietal lobe. An experimentally induced lesion in the medulla leading to natriuresis and polyuria has been noted. . However, on account of the variety of intracranial lesions and quantity of reported cases of CSWS, interpretation of anatomic evidence is rather difficult. [6]

Differentiation of SIADH and CSWS

Owing to the considerable overlap of the laboratory findings, determination of ECF volume remains the primary means of distinguishing these disorders. ECF volume is increased in SIADH, whereas it is low in CSWS. [10]

Clinical findings that support a diagnosis of CSWS include orthostatic changes in blood pressure and pulse, dry mucous membranes, flat neck veins, weight loss and negative fluid balance. [10] A water input:output ratio <1 shows a negative water balance. A low pulmonary capillary wedge pressure (PCWP) (<8 mm Hg) or a low central venous pressure (CVP) (<6 mm Hg) can be useful in the assessment of volume contraction. [6.] The CVP closely correlates with changes in total blood volume in patients with normal cardiac and pulmonary function. Sivakumar et al advocate the use of CVP monitoring to guide the management of hyponatremia. [6]

	CSWS	**SIADH**
Plasma volume	↓	↑
Salt balance	Negative	Variable
Urine Output [17]	↑	↓
Dehydration	Present	Absent
Body weight	↓	↑ or no change
PCWP	↓	↑ or normal
CVP	↓	↑ or normal
Hematocrit	↑	↓ or no change
Osmolality	↑ or normal	↓
BUN: creatinine ratio	↑	Normal
Serum protein concentration	↑	Normal
Urine sodium concentration	↑↑	↑
Serum potassium concentration	↑ or no change	↓ or no change
Serum uric acid concentration [10]	↓	↓
FEUA[18]	↑↑ and remains ↑↑even after correction of hyponatremia	↑↑ but gets normal after correction of hyponatremia
Fractional Na excretion[17]	↑	↑
Treatment[17]	Fluid and salt, fludrocortisone	Fluid restriction, demeclocycline

Studies of volume status, using isotope-dilution techniques, can be performed at the bedside. Diminished plasma volume (<35 ml/kg) is a central feature of CSW. Nelson et al. reported an average plasma volume of 30.3 ml per kilogram in hyponatremic patients with intracranial disease, which is 26% less than that for normonatremic control patients. A decrease in total blood volume (<60 ml/kg) is also associated with CSWS. [6]

Laboratory findings that are useful include evidence of hemoconcentration, as reflected by an increased hematocrit and serum albumin concentration, and the finding of a raised serum bicarbonate concentration. [10] Blood urea nitrogen (BUN) increases in patients with volume contraction as is seen in CSWS, whereas in patients with SIADH with volume expanded state, the BUN is usually on the lower side. This, however, is not always observed and not very helpful. [19] As mentioned above, uric acid levels are depressed in patients with SIADH, which reflects the slight increase in ECF volume. By contrast, uric acid levels in patients with hyponatremia occurring in the setting of decreased ECF volume are either normal or slightly increased. But, serum uric acid levels in CSWS tend to be unexpectedly low [10]

Hypouricemia and increased fractional urate excretion might be a common feature of intracranial disease in general. As for the distinction between the two, although correction of the serum Na^+ concentration in SIADH leads to a normalization of uric acid handling by the kidney, hypouricemia and increased renal uric acid excretion remain persistent findings following the correction of the serum sodium concentration in CSWS. [10, 18, 19]

Fractional excretion of uric acid =
(urinary uric acid x serum creatinine) / (serum uric acid x urinary creatinine) x 100%

Normally FEUA should be <10 %. [18] Age and gender plays significant role in the renal handling of uric acid. FEUA is very high in children and reaches to a static level only after the age of 20 years; females at 12% and males at 8%.[41]

Serum ADH and ANP levels are not helpful in distinguishing between CSWS and SIADH. ANP levels have been observed to be elevated or normal in CSWS. [6] Although elevated ADH levels can be diagnostic of SIADH with ADH usually being depressed in CSWS, ADH levels can be misleading. Stress, pain, and increased intracranial pressure which are all common features of acute intracranial disease, can promote secretion of ADH. SIADH and CSWS have been reported to successively occur in the same patient, particularly after SAH. Thus, a water-load test may be performed to confirm a diagnosis of SIADH, but it is important to recall that CSWS may occur after SIADH. Also, the reverse situation may occur; ADH secretion may appropriately increase, despite the presence of hyponatremia, in response to volume depletion. [6]

SIADH may immediately occur after an acute intracranial insult, but prolonged hyponatremia is associated with persistent elevation of plasma ANP. Yamamoto et al. described a patient with hyponatremia after SAH. Both plasma ADH and ANP levels were elevated above the normal range 5 days after hemorrhage, but only ANP remained elevated at 13 and 28 days, associated with a prolonged period of hyponatremia.[6]

Differentials

Certain conditions need to be ruled out before labeling SIADH or CSWS as the cause for hyponatremia. SIADH can be induced by medications. Hypothyroidism can masquerade as SIADH. Adrenal insufficiency is another important consideration. Adrenal failure and hypothyroidism usually develop slowly. Other causes include fluid overload or extracellular fluid depletion from gastrointestinal (GI) or renal loss of sodium. The insensate fluid loss also contributes to hyponatremia, assisted by both dermal and respiratory losses. [5]

It need not be over emphasized that hyperglycemia, excess mannitol, hypertriglyceridemia and hyperproteinemia must always be ruled out. [7] As has already been mentioned above, hypothyroidism and adrenal insufficiency could occur as a part of neuroendocrine dysfunction after a TBI. The prevalence of hypopituitarism was 42.7%, ranging from 28 to 68.5% in the different series evaluating patients who recovered from

the acute phase post-TBI. Of those hypo-pituitary patients, hypothyroidism was noted in 90% and adrenal insufficiency in 58%. [1]

Acute illness or trauma can induce alterations in thyroid hormone equilibrium within hours. Although thyroid stimulating hormone (TSH) usually remains normal, circulating thyroxine (T4) levels may be reduced or normal, while tri-iodothyronine (T3) rapidly drops, partly due to decreased T4 conversion to T3 and/or increased thyroid hormone turnover. These changes are consistent with the occurrence of low-T3 syndrome. As the patients recover, thyroid hormones return slowly to normal over weeks. In TBI patients, lower TSH levels may be present in the early phase after injury, suggesting that the reduced production of thyroid hormones may have a central cause. A low T4 in the absence of elevated TSH indicates secondary hypothyroidism. A recent evaluation of 50 patients in the acute phase post-TBI showed central hypothyroidism in one (5%).

Central hypothyroidism was also demonstrated in 15% of critical care patients with moderate to severe TBI. TSH deficiency has been found in TBI patients evaluated by assessing either basal hormone levels (1–22%) or response to TRH stimulation (4.5%). A previous series demonstrated a very high occurrence of TSH deficiency among TBI patients with hypopituitarism, suggesting TBI as an important cause of otherwise unexplained central hypothyroidism.[1]

The mechanism by which hypothyroidism leads to hyponatremia includes decreased cardiac output and GFR and increased ADH secretion in response to hemodynamic stimuli. [36]

Adrenal insufficiency has been found in 16% of patients during the early phase post-TBI, suggesting post-traumatic damage at the hypothalamic–pituitary level. However, the diagnosis of glucocorticoid deficiency is challenging during the acute phase, due to the difficulty in selecting a reliable test for assessing cortisol secretion. Corticoptropin function is assessed by measuring serum cortisol concentration from 0800 to 0900 h on two or more occasions. A serum cortisol level <3 μg/dl is characteristic of adrenal insufficiency, while a serum cortisol >18 μg/dl defines normal cortisol secretion. When

the morning cortisol value is persistently in the lower limit of the normal range, a test of ACTH reserve should be performed, in order to demonstrate the presence of a subclinical corticotrope deficiency. Corticotropin deficiency has been demonstrated in less than 10% of TBI patients.[1]

As endocrine evaluation and definition of normal or impaired corticotropin secretion in TBI patients is still a matter of debate, [1] of clinical importance in recognizing adrenal insufficiency is hyperkalemia associated with the hyponatremia secondary to a loss of mineralocorticoid activity at the kidney, causing urine sodium loss, impaired excretion of potassium, and hydrogen ion retention. [5]

Management of hyponatremia

Appropriate fluid management of patients with TBI presents a challenge for many clinicians. Many of these patients may receive osmotic diuretics for the treatment of increased intracranial pressure or develop sodium disturbances, which act to alter fluid balance. However, establishment of fluid balance is extremely important for improving patient outcomes after neurologic injury. [20]

Whereas patients with persistent asymptomatic hyponatremia require slow-paced management, those with symptomatic hyponatremia must receive rapid but controlled correction. Although morbidity varies widely in severity, serious complications can arise from the disorder itself as well as from errors in management. [7]

Formulas for Use in Managing Hyponatremia [7]

Formula		**Clinical Use**
Change in serum Na^+ =	$\frac{\text{infusate } Na^+ - \text{serum } Na^+}{\text{total body water} + 1}$	Estimate the effect of 1 L on any infusate serum Na^+

Change in serum Na^+ =	(infusate Na^+ + infusate K^+)—serum Na^+ ——————————— total body water +1	Estimate the effect of 1 L of any infusate containing Na^+ and K^+ on serum Na^+

The estimated total body water (in liters) is calculated as a fraction of body weight. The fraction is 0.6 in children; 0.6 and 0.5 in non-elderly men and women, respectively; and 0.5 and 0.45 in elderly men and women, respectively. [7]

Characteristics of infusates: [7]

Infusate	**Infusate Na^+**	**Extracellular—Fluid Distribution**
	mmol/L	%
5% sodium chloride in water	855	100†
3% sodium chloride in water	513	100†
0.9% sodium chloride in water	154	100
Ringer lactate solution	130	97
0.45% sodium chloride in water	77	73
0.2% sodium chloride in 5% dextrose in water	34	55
5% dextrose in water	0	40

†In addition to its complete distribution in the extracellular compartment, this infusate induces osmotic removal of water from the intracellular compartment.

Symptomatic Hypotonic Hyponatremia[7]

Patients who have symptomatic hyponatremia with concentrated urine (osmolality, >200 mOsm/ kg of water) and clinical euvolemia or hypervolemia require infusion of hypertonic saline. On the other hand, most patients with hypovolemia can be treated successfully with isotonic saline. Patients with symptomatic hyponatremia and dilute urine (osmolality, <200 mOsm per kilogram of water) but with less serious symptoms usually require only water restriction and close observation. Severe symptoms (e.g., seizures or coma) call for infusion of hypertonic saline.

Patients with seizures also require immediate anticonvulsant-drug therapy and adequate ventilation. Hormone replacement therapy should be given to patients with suspected hypothyroidism or adrenal insufficiency. Physiologic considerations indicate that a relatively small increase in the serum sodium concentration, on the order of 5 percent, should substantially reduce cerebral edema. Even seizures induced by hyponatremia can be stopped by rapid increases in the serum sodium concentration that average only 3 to 7 mmol per liter. Most reported cases of osmotic demyelination occurred after rates of correction that exceeded 12 mmol per liter per day were used, but isolated cases occurred after corrections of only 9 to 10 mmol per liter in 24 hours or 19 mmol per liter in 48 hours. After weighing the available evidence and the all-too-real risk of overshooting the mark, a targeted rate of correction that does not exceed 8 mmol per liter on any day of treatment is recommended. Remaining within this target, the initial rate of correction can still be 1 to 2 mmol per liter per hour for several hours in patients with severe symptoms. Should severe symptoms not respond to correction according to the specified target, this limit be cautiously exceeded, since the imminent risks of hypotonicity override the potential risk of osmotic demyelination. Recommended indications for stopping the rapid correction of symptomatic hyponatremia are the cessation of life-threatening manifestations, moderation of other symptoms, or the achievement of a serum sodium concentration of 125 to 130 mmol per liter (or even lower if the base-line serum sodium concentration is below 100 mmol per liter).. Although faster rates of correction can be

tolerated safely by most patients with acute symptomatic hyponatremia, there is no evidence that such an approach is beneficial.

Asymptomatic Hypotonic Hyponatremia[7]

For certain patients with asymptomatic hyponatremia, the main risk of complications occurs during the correction phase. This is true of patients who stopped drinking large amounts of water and those who underwent repair of a water-excretion defect (e.g., repletion of extracellular-fluid volume and discontinuation of drugs that cause the condition). If excessive diuresis occurs and the projected rate of spontaneous correction exceeds that recommended for patients with symptomatic hyponatremia, hypotonic fluids or desmopressin can be administered.

By contrast, there is no such risk associated with the asymptomatic hyponatremia that accompanies edematous states or the persistent syndrome of inappropriate secretion of antidiuretic hormone because of the prevailing defect of water excretion. Water restriction (to <800 ml per day) is the mainstay of long-term management, with the goal being induction of negative water balance. Loop, but not thiazide, diuretics reduce urine concentration and augment excretion of electrolyte-free water, thereby permitting relaxation of fluid restriction. In the syndrome of inappropriate secretion of antidiuretic hormone, but not in edematous disorders, loop diuretics should be combined with plentiful sodium intake (in the form of dietary sodium or salt tablets), a treatment that augments water loss. If these measures fail, 600 to 1200 mg of demeclocycline per day can help by inducing nephrogenic diabetes insipidus. Monitoring of renal function is required, because demeclocycline has nephrotoxic effects, especially in patients with cirrhosis. Moreover, the drug imposes the risk of hypernatremia in patients who do not take in sufficient water. Alternatively conivaptan can also be used, which is a new drug that has been approved for the treatment of hyponatremia that is not responsive to fluid restriction.

Nonhypotonic Hyponatremia[7]

Corrective measures for nonhypotonic hyponatremia are directed at the underlying disorder rather than at the hyponatremia itself. Administration of insulin is the basis of treatment for uncontrolled diabetes, but deficits of water, sodium, and potassium should

also be corrected. Furosemide hastens the recovery of patients who absorb irrigant solutions; if renal function is impaired, hemodialysis is the preferred option.

In a synopsis, treatment of SIADH usually consists of continuous fluid restriction to 500 to 1000 ml daily until the serum sodium value normalizes. In patients with severe, symptomatic hyponatremia, hypertonic saline may be slowly administered. In CSWS intravenous hydration with normal saline (0.9% NaCl), hypertonic saline (3% NaCl), or oral salt may be used alone or in combination, depending on the severity of hyponatremia and the ability of the patient to tolerate enteral administration. Blood products are useful for volume expansion if anemia is also present. Fosset advocates volume replacement with colloids and whole blood; colloids act as volume expanders by absorbing interstitial and third-spaced fluid. The goal of water replacement is to match urine losses. [6]

Isotonic saline is unsuitable for correcting the hyponatremia of the syndrome of inappropriate secretion of antidiuretic hormone; if administered, the resulting rise in serum sodium is both small and transient, with the infused salt being excreted in concentrated urine and thereby causing a net retention of water and worsening of the hyponatremia. [7]

Wijdicks et al. argue that increasing salt intake during CSWS only further enhances sodium excretion. Prevention of volume depletion by reducing renal sodium excretion may be more appropriate. The mineralocorticoid fludrocortisone acetate directly acts on the renal tubule to enhance sodium reabsorption. While the drug is being used one must be cautious about side effects and complications of fludrocortisone including pulmonary edema, hypokalemia, and hypertension. But still the efficacy of this drug in CSWS remains to be proven. [6]

Another alternative is the intravenous administration of urea and saline, which has potential as a treatment for both CSWS and SIADH. Reeder and Harbaugh treated patients with hyponatremia caused by intracranial disease by administering urea and saline. The regimen consisted of 40 gm of urea dissolved in 100 to 150 ml of normal saline administered by intravenous drip every 8 hours and an intravenous infusion of normal saline at 60 to 100 ml per hour for 1 to 2 days. The side effects of intravenously

administered urea include headache, nausea, and vomiting. They theorized that urea induces a mild osmotic diuresis and depresses urinary sodium excretion, whereas supplemental salt restores sodium deficits. They advocated the use of this treatment for both SIADH and CSWS. This regimen would be particularly useful in situations in which the diagnosis is not clear or in which CSWS quickly occurs after SIADH. [6]

Treatment of hyponatremia in SAH is quite different in a sense that fluid restriction cannot be used as a treatment measure since it is likely to deteriorate the adverse effects of vasospasm, rather must be strictly avoided.[21, 22] Administration of isotonic fluid can prevent volume contraction but not hyponatremia. Use of slightly hypertonic sodium chloride (1.5% sodium chloride) at rates above maintenance requirements usually is efficacious for SAH-induced hyponatremia. [22]

Studies on TBI, SIADH and CSWS

Studies on SIADH post-TBI have yielded conflicting results, showing a prevalence ranging from 2.3 to 36.6%. [1]

Mori et al performed a retrospective analysis of 298 patients of TBI mostly mild to moderate. 50 (16.8%) presented hyponatremia during the time course. Hyponatremia was associated with longer hospital stay ($P < .001$) and bad outcome ($P = .02$). Among these 50 patients, 37 recovered from the hyponatremia with simple sodium supplementation. The remaining 13 patients presented massive natriuresis and required additional sodium retention therapy. Hydrocortisone was used as a sodium retention therapy. It statistically reduced the amount of sodium excretion ($P = .002$) and urine volume ($P < .01$) and returned the serum sodium level to a normal value. Though the total percentage of hyponatremia was 16.8%, among the patients with intracranial bleeding, the percentage of hyponatremia was up to 27.0%. Surprisingly, in the patients with cerebral contusions, 47.9% presented hyponatremia during the time course. In addition, the patients with chronic subdural hematoma presented hyponatremia in 15.9% of cases, which had never previously been indicated. Regarding the timing of hyponatremia, two peaks were noted. Most patients presented hyponatremia within 3 days of trauma; however, some patients

presented hyponatremia after 8 days. Among the 50 patients with hyponatremia, 10 patients (20.0%) revealed a mean arterial blood pressure of below 80 mm Hg when hyponatremia was detected; however, no value was less than 70 mm Hg. Regarding the levels of hematocrit, blood urea and serum potassium, no difference was seen between the patients with and without hyponatremia No patient was measured for pituitary hormone levels among these patients. [8]

In a study done by Steinbok et al. eighty-eight patients with craniocerebral trauma were studied prospectively to assess the effects of the injury on sodium and water balance. Abnormalities of serum sodium and osmolality occurred in 11 of the 76 patients who were on the study more than 24 hours, and the incidence of these abnormalities was directly related to the severity of the craniocerebral injury. Hyponatremic hypo-osmolar states were as frequent as were hypernatremia and serum hyperosmolality. The major cause of the hyponatremia was inappropriate antidiuretic hormone secretion; hypernatremia was due to dehydration and occurred predominantly in comatose patients with increased insensible fluid losses associated with pyrexia. They recommend that the initial fluid intake after craniocerebral trauma be kept between 1500 and 1800 ml/24 hours and that further fluid management be dictated by repeated serum electrolyte determinations. The electrolyte balance should be monitored continuously after a significant head injury for up to 2 weeks, because hyponatremic states sometimes develop more than 1 week after injury. The serum alcohol was measured on admission, and the level of serum alcohol correlated well with the serum osmolality on admission; thus, the degree of elevation of serum osmolality was a very good guide to the serum alcohol level. However, there was no statistically significant correlation between alcohol intoxication or chronic alcoholism and the late development of serum sodium and osmolality disturbances. [24]

In a study by Born et al, based on 109 patients with severe head injury who had a GCS equal to or less than 7 and a Liège coma score equal to or less than 12 in the first 24 hours, SIADH seemed to be a frequent complication of severe craniocerebral trauma, discovered in 33% of patients. On the other hand, diabetes insipidus was rarely diagnosed

(2.8%). They propose, in cranial trauma, to subdivide SIADH into two clinical forms: an early syndrome (5%) that becomes apparent towards the second day, significantly associated with lesions at the base of the skull; and a delayed syndrome that occurs at the end of the first week and is related to different factors inherent in intensive care procedures. Surgical intervention, in the case of acute craniocerebral trauma, did not result in a higher frequency of SIADH.[25]

In a study done by Doczi et al[38.] the authors report a review of 1808 patients admitted for the treatment of craniocerebral injuries. Eighty-four (4.6%) developed SIADH. SIADH occurred in 0.6% of the patients with mild head injury, 10.6% of those with moderate head injury, and 4.7% of the patients with severe head injury. In this study, diagnosis of SIADH was made based on laboratory criteria without consideration of volume status, raising the possibility that some of the patients diagnosed with SIADH actually might have had CSW. [6]

In a series of TBI patients on Beautmount hospital, Ireland, presented by Thompson, plasma sodium concentrations < 130 mmol/l occurred in 8% of patients.[16]

Evaluation of DI was performed by Agha et al. in 102 consecutive patients (85 males) who suffered severe or moderate TBI. Twenty-two patients (21.6%) developed DI in the immediate post-TBI period. Permanent DI was present in 6.9% of patients who survived severe or moderate TBI. 13 patients (12.9%) had SIADH, which persisted in one patient, and one other patient developed CSWS. Patients in the acute and permanent DI groups were more likely to have more severe TBI, compared with the rest of the cohort ($P <$ 0.05). A significant association between acute posttraumatic DI and more severe TBI was noted, as indicated by lower GCS scores or CT evidence of raised ICP due to cerebral edema. Because both variables are markers of the severity of TBI, they concluded that acute DI is associated with more severe trauma. [11]

Ishikawa et al, reported cases of severe hyponatremia that developed within 2 weeks of head injuries in three elderly patients. Before the head injuries occurred, normal serum levels of sodium had been found in two of the three patients. Hyponatremia (105 to 117 meq/L) was associated with persistently increased urinary excretion of sodium. The patients appeared dehydrated and had lost weight. The mean plasma level of antidiuretic hormone was 5.0 +/- 1.6 (SD) pg/mL, which was relatively high despite decreased osmolality. Plasma renin activity was suppressed to 0.25 +/- 0.13 ng/mL X h, and plasma aldosterone levels measured low-normal or normal. Plasma renin activity and plasma aldosterone levels remained unchanged after the patients were given furosemide and placed in an upright position. The hyponatremia promptly resolved after the administration of fludrocortisone acetate, 0.1 to 0.4 mg/d. These observations indicate that severe hyponatremia occurs in elderly persons rapidly after head injuries, that it responds well to mineralocorticoid hormone therapy, and that both central nervous system and renal components may be involved in the mechanisms of action of the disorder. [26]

Hyponatremia has been reported even in a case of mild head injury, though the patient was asymptomatic and showed no clinical deterioration. [27]

Kumar et al, reported a case of delayed SIADH after head injury. 38 yr-old man who had bilateral frontal lobe contusions and subarachnoid hemorrhage, improved with conservative treatment but presented one year later with generalized tonic-clonic seizures, sodium level 119 mmol/L and other findings consistent with SIADH. A computed tomographic scan of the brain showed encephalomalacia of both frontal lobes. Patient improved simply with fluid restriction. [28]

Even in pediatric age group CSWS has been reported following head injury. In a case report by Kawajiri et al. a 4-year-old boy with a linear fracture of the bilateral parietal bones, and subarachnoid hemorrhage of the tentorium of the cerebellum developed CSWS on 6th day for which the patient had to be treated with fludrocortisone acetate and finally the patient was discharged without any neurological deficits. [29]

Some author view that CSWS is actually much less common than the literature presents. Three fallacies concerning cerebral salt wasting are stressed: first, cerebral salt wasting is a common disorder; second, hyponatremia should be one of its diagnostic features; and third, most patients have a negative balance for Na when the diagnosis of cerebral salt wasting is made. The cause for natriuresis could be: first, a severe degree of extracellular fluid volume expansion could down-regulate transporters involved in renal Na resorption; second, an adrenergic surge could cause a pressure natriuresis; and third, natriuretic agents might become more potent when the effective extracellular fluid volume is high. Since a cerebral lesion and a large natriuresis without a known stimulus to excrete so much sodium constitute its essential two elements of CSWS, there is a diagnostic problem because it is difficult to confirm that a stimulus for the renal excretion of Na is absent. [30]

While CSWS has been regarded as a misnomer of the SIADH, some authors take the position that CSWS does exist and might be more common than SIADH. Clinical assessment of extracellular volume is accurate in about 50% of these patients. Determination of serum urate and fractional excretion rates of urate can differentiate one group from the other. In both groups, hyponatremia coexists with hypouricemia and increased fractional excretion of urate. When the hyponatremia is corrected by water restriction, hypouricemia and elevated FEurate correct in SIADH but persist in CSWS. Persistent hypouricemia and elevated FEurate were commonly noted with pulmonary and/or intracranial diseases. The absence of intracranial diseases in some patients suggests that renal salt wasting might be a more appropriate term than CSWS. A review of renal/CSWS reveals three studies involving hyponatremic neurosurgical patients who had decreased blood volume, decreased central venous pressure, and inappropriately high urinary sodium concentrations in the majority of them, suggesting that CSWS was more common than SIADH in neurosurgical patients. [19]

The available studies indicate that CSW occurs as frequently as or more frequently than SIADH in neurosurgical patients and some 14% of patients with SIADH have no detectable abnormalities in ADH secretion [6]

As demonstrated in a case report by Zafonte et al. confusion in the diagnosis of SIADH and CSWS can be extremely deleterious, especially in cases of subarachnoid hemorrhage where if CSWS is misinterpreted for SIADH and treated with fluid restriction, adverse effects of vasospasm might in fact worsen. [21]

Nelson et al. reported a study of 12 patients with intracranial disease (SAH, head injury, or craniotomy for unruptured aneurysm) who met the traditional laboratory criteria for SIADH. They performed blood volume analyses and found that 10 of the 12 patients had significant decreases in red blood cell mass, plasma volume, and total blood volume when compared with controls. These findings were consistent with the original concept of CSWS, whereby an inability of the kidneys to conserve sodium leads to progressive salt wasting and volume depletion. The authors theorized that volume depletion stimulates ADH release, leading to water retention and, along with concomitant salt loss, hyponatremia. They emphasized that serum and urine electrolytes and osmolalities may be the same in patients with SIADH or CSWS, necessitating consideration of the volume status of each patient before beginning fluid restriction. They warned that fluid restriction in patients who are volume depleted could lead to hemoconcentration and increased blood viscosity and jeopardize cerebral perfusion. [31]

Further support for CSWS came from Wijdicks et al. in a study of sodium balance and volume status in 21 patients after aneurysmal SAH. Plasma volume decreased by more than 10% in 11 of the 21 patients. Ten of the 11 patients with decreased volumes had negative sodium balances; 6 also had hyponatremia. Decreased plasma volume was accompanied by an increase in blood urea nitrogen and a decrease in body weight. This demonstration of hyponatremia, natriuresis, and volume depletion was incompatible with true SIADH. [32]

Vingerhoets and de Tribolet studied 256 patients with severe brain injury. Six patients met the criteria for SIADH; three in the first 3 days after injury and three after more than a week. Plasma ADH levels were measured and found to be elevated only in the group with“early hyponatremia.” In the patients with “late hyponatremia,” plasma ADH levels

were normal regarding serum osmolality. Moreover, two of the patients with late hyponatremia did not respond to fluid restriction. The authors theorized that elevated levels of ADH can occur after brain injury because of a number of factors that promote ADH release, such as hypovolemia caused by fluid or blood loss, stress, pain, medications, and increased intracranial pressure. This hypersecretion of ADH, although not physiologically "inappropriate," may lead to hyponatremia. Hyponatremia in the second week after brain injury however is more likely to be caused by CSWS than SIADH. [6]

More evidence in favor of CSWS was provided by Sivakumar et al. in a series of 21 neurosurgical patients with hyponatremia who met the criteria for SIADH. The patients had a variety of intracranial disorders. Volume status was assessed by measuring CVP and total blood volume; hematocrit was observed. All 21 patients were hypovolemic, with or without anemia. Hyponatremia was corrected in all patients after administration of isotonic saline and oral salt (and whole blood if anemic). The presence of volume depletion, and the response to volume supplementation rather than restriction, is more compatible with CSWS than SIADH. [33]

To investigate the suggestion that fluid restriction may actually harm patients with hyponatremia, Wijdicks et al. performed a retrospective study of 134 patients after aneurysmal SAH. Forty-four patients were hyponatremic, and 25 of these met the criteria for SIADH. Twenty-six patients were treated with fluid restriction, and cerebral infarctions developed in 21 (81%). The rate of cerebral infarction was significantly higher among the patients with hyponatremia versus the patients with normal serum sodium levels. These findings provided indirect evidence that hyponatremia in patients with SAH is more likely to be the result of CSWS, in which case fluid restriction exacerbates underlying volume depletion, leading to an increased risk of cerebral infarction.[6]

Hyponatremia following SAH occurs in 10-34% of cases. Elevated levels of ANP and SIADH have been implicated in recent studies of post-SAH hyponatremia.[22]

Sherlock et al. did a study on hyponatraemia following SAH. A retrospective case-note analysis of all patients with SAH admitted to Beaumont Hospital between January 2002 and September 2003. 316 cases of SAH were substantiated by CT scan and angiogram findings. Hyponatraemia was defined as plasma sodium < 135 mmol/l. 179 patients (56.6%) developed hyponatraemia and 62 (19.6%) developed significant hyponatraemia (plasma sodium < 130 mmol/l). The etiology of significant hyponatraemia was the SIADH 69.2%, CSWS 6.5%, hypovolaemic hyponatraemia 21%, hypervolaemic hyponatraemia 4.8% and mixed CSW/SIADH 4.8%. Hyponatraemia was associated with longer hospital stay (24.0 +/- 2.6 vs. 11.8 +/- 0.8 days, P < 0.001) but did not affect mortality (P = 0.07). Hyponatraemia developed more than 7 days following SAH in 21.4% .They concluded that hyponatraemia is common following SAH and is associated with longer hospital stay. SIADH is the commonest cause of hyponatraemia after SAH. Delayed hyponatraemia is common, and has implications for early discharge strategies. [34]

Sayama et al did a study on hyponatremia in subarachnoid hemorrhage (SAH) patients. Results were suggestive of an association between the site of bleed and the occurrence of CSWS. His study included 55 patients with ruptured A-com aneurysms, 65 with ruptured internal carotid artery (ICA) aneurysms, and 49 with ruptured middle cerebral artery (MCA) aneurysms. Hyponatremia occurred in 51% of patients with A-com aneurysms and in 18% of patients with MCA aneurysms. Severe hyponatremia (Na < 130 mEq l-1) occurred in 29% in the A-com group, 6% in the ICA group, and 6% in the MCA group. The A-com aneurysm group had a significantly higher incidence of mild hyponatremia ($p < 0.01$) and severe hyponatremia ($p < 0.001$) than other groups. Day of onset for hyponatremia was 10.6 +/- 5.8 and in most patients hyponatremia resolved within 28 days Hyponatremia occurred more often with A-com aneurysms, possibly because of vasospasm around the A-com or hydrocephalus causing hypothalamic dysfunction. [35]

Objectives

General: To study the etiology and incidence of hyponatremia in patients with traumatic brain injury, including its correlation with initial severity and final outcome.

Specific:

- To identify the incidence of hyponatremia in TBI.
- To identify the timing of hyponatremia in TBI.
- To identify the proportion of cases of hyponatremia attributable to syndrome of inappropriate anti diuretic hormone (SIADH), cerebral salt wasting syndrome (CSWS).
- To study the correlation of initial clinical severity of TBI with hyponatremia.
- To study the correlation of initial radiological severity of TBI with hyponatremia.
- To study the effect of hyponatremia in the outcome of patients with TBI.

Research questions

- How common is hyponatremia in patients with traumatic brain injury?
- What is the timing of hyponatremia in TBI?
- Is there any correlation between clinical and radiological severity of TBI to the occurrence and timing of hyponatremia?
- What is the relative incidence of SIADH and CSWS?
- Is hyponatremia associated with prolonged hospital stay and poor outcome of the patient even after a proper diagnosis and respective management?

Research Methodology

Research method: quantitative

Study variables:

- Independent variables: age distribution, sex distribution, GCS at the time of presentation, Rotterdam CT score, mechanism of head injury, associated co-morbidity.
- Dependent variable: incidence of hyponatremia/ SIADH/ CSWS, timing of hyponatremia, duration of hospital stay, glasgow outcome scale at discharge.

- Confounding variable: associated co-morbidity and medication induced hyponatremia

Type of study: Prospective, descriptive and analytical.

Study site: National Institute of Neurological and Allied Sciences, Bansbari, Kathmandu.

Target population: Patients admitted with diagnosis of TBI.

Sampling method/ sample size/ sampling frame: Universal sample with inclusion and exclusion criteria defined.

Inclusion criteria:

- Patients above 20 years irrespective of their gender.
- Patient attending to this hospital upto three days post-TBI; since this is a referral centre for patients from all over Nepal, a delay of three days had to be considered.

Exclusion criteria:

- Patients with established renal, thyroid or adrenal diseases prior to the TBI as they have profound effect on fluid and electrolyte balance.
- Patient presenting beyond 3 days post-TBI.
- Patients less than 20 yrs; till the age of 20 years, FEUA levels can be variable.
- Cases with associated spinal cord injuries, since they alone have been reported to cause CSWS.

Data collection and Research Frame:

- All patients presenting from April to September 2008 who fulfilled the inclusion criteria were included in the study.
- Consent was taken from patients at the time of admission as far as possible.
- Preformed structured format were used to make pertinent clinical, radiological and laboratory documentation.
- Severity of TBI was classified as mild, moderate and severe based on GCS; 13-15, 9-11 and 3-8 respectively.

- CT scan was done in all the patients and CT grading was noted.
- Baseline investigations were done in all the patients. This included hemoglobin, random blood sugar, serum albumin, Na, K, urea, and creatinine.
- Sodium levels were checked daily for 14 days or till the patient was discharged, whichever was earlier.
- CVP catheter was inserted in all patients who underwent surgical intervention. In those with conservative management, catheter was inserted after the development of hyponatremia. Following every insertion of CVP, proper catheter positioning was confirmed with a chest X-ray; with radiopaque dye if essential.
- CVP 6-10 cm was considered as normal measurement.
- Sodium level below 130 mEq/L was considered as hyponatremia.
- Upon the diagnosis of hyponatremia, further investigation were performed with the aim of differentiating SIADH and CSWS. These included serum/ urinary creatinine, serum/ urinary uric acid, serum albumin and serum urea. In addition some baseline investigations were repeated, as per the requirement for management.
- Regarding the treatment of hyponatremia, fluid restriction in patients with head injury was avoided, irrespective of the diagnosis. All patients were treated with oral salt supplementation and intravenous normal saline after detection of hyponatremia. If patient did not respond to this therapy and had high CVP then moderate fluid restriction upto 1500 ml/day was done. In patient with low CVP, fludrocortisone was used if initial therapy did not correct hyponatremia.

Pre-testing: Pre-testing was done in three patients and accordingly, proforma was slightly modified.

Validity and reliability:

- Clinical documentations and diagnosis were based on predefined conditions.
  eg. Clinical classification of TBI, radiological classification of TBI, hyponatremia etc.

- Definitions of the clinical conditions and determination of necessary assessment, investigation and intervention had been made after a thorough literature review.
- Patients under study were managed by experienced neurosurgical team in the tertiary medical centre.
- The neurosurgical team supervised and guided the research process.
- All investigations were done in the same laboratory.

Biases

- Bias in information collection was minimized with the use of structured pre-tested questionnaires.
- Observer bias: All definitions were objective so as to minimize this.
- Selection bias: Universal sample used but inclusion and exclusion criteria are strictly defined to minimize this.
- Measurement bias: Since the study relies heavily on laboratory criteria, errors of measurement could have a significant mark.
- Confounding: as previously mentioned.

Limitation of the study

- Study conclusions rely significantly on the accuracy of the laboratory reporting. Unexpected results regarding measurement of FEUA could be a result, if any, of such erroneous laboratory measurements.
- There was slight variation in the period of observation of each patient, which could have a negligible influence on incidence of hyponatremia.
- Mild head injuries with no significant abnormality on CT scan have not been included in the study. Incidence of hyponatremia presented by this study won't thus be a representative of head injury in entirety but only that of high risk group.
- Study was done over a period of six months. Total 40 patients were enrolled in the study. Expected sample size was not met.

- Diagnosis of SIADH and CSWS has been made solely based on CVP measurement. Traditional diagnostic criteria have not been used. Hence the accuracy of diagnosis can't be ascertained.

Data management/ analysis

- Strict questionnaire based data collection as far as possible
- SPSS was used for the analysis and diagrammatic representation of the findings.

Ethical considerations/ Informed Consent:

- Human participants were needed for the research.
- Informed written consent was taken.
- Patients were assigned a particular diagnosis with appropriate clinical and laboratory evaluation. They receive treatment that has been best established till date for the particular condition. So regarding the aspect of management patient will not be subjected to any clinical harm because of the study.
- Investigations that were performed solely for the research purpose was paid from the research fund. This included the estimation of FEUA (measurements of serum/urine creatinine and uric acid). Daily sodium level monitoring is a routine protocol in this hospital, hence it was not considered for recompense.

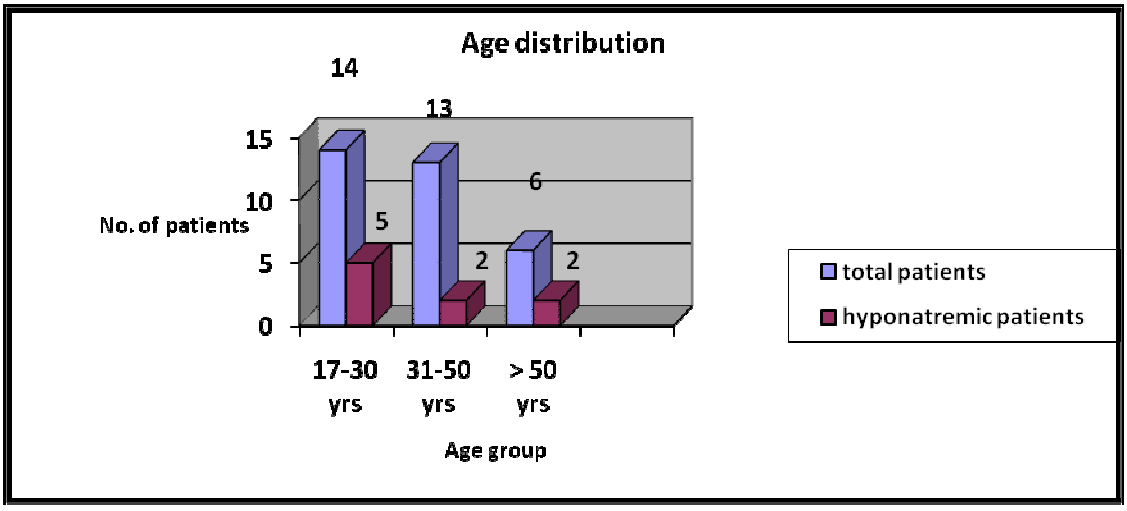
Results

A total of 40 patients were enrolled in the study, out of which seven patients were excluded as they had hospital stay of less than a week because of various reasons like early mortality, transfer to other centres, or had asscociated medical ailments that could produce hyponatremia. Out of 33 patients that remained for the analysis, hyponatremia was seen in nine patients within the period of two weeks.

Age distribution

The mean age was 37.42 (19-70) yrs with Standard Deviation (SD) of 15.33. Age group of 17-30 and 31-50 had 42.4 and 39.4% patients, with least being 18.2% in age group of >50. Among the hyponatremic patients, mean age was 38.44 (23-69) years with SD 16.4, and 17-30 age group had maximum, five (55.6%) patients.

Figure 1. Age distribution of total and hyponatremic patients



Sex distribution

There were a total of 26 males and seven females. Male to female ratio was 3.7:1. Among hyponatremic patients, seven were males and two were females. Male to female ratio was 3.5:1.

Figure 2a. Sex distribution among total patients

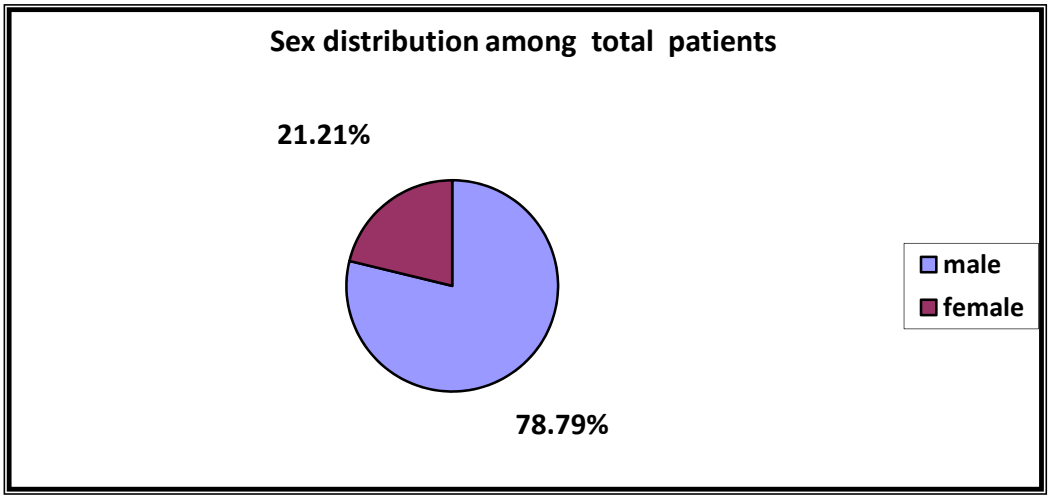
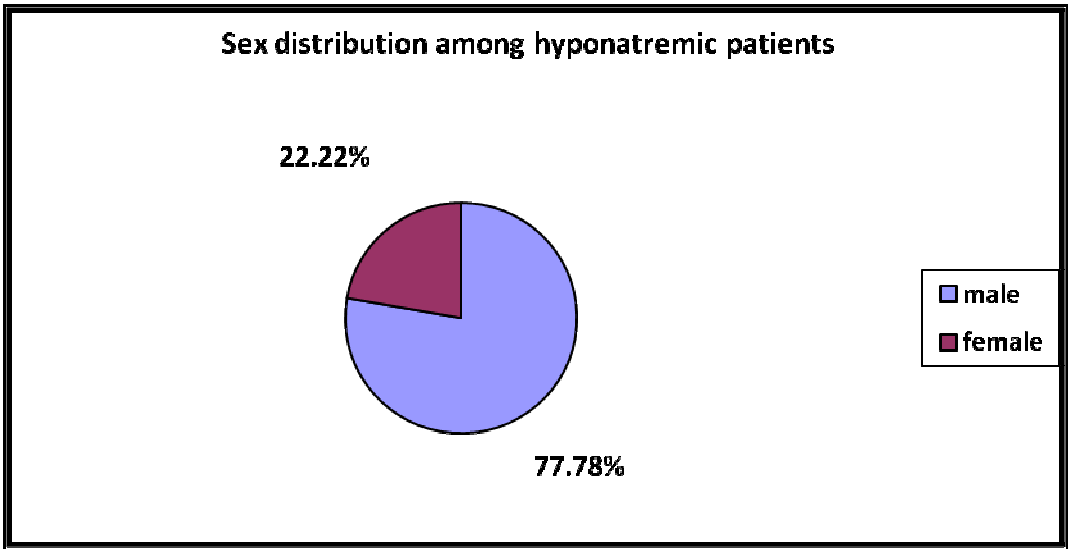


Figure 2b. Sex distribution among hyponatremic patients



Severity based on GCS at the time of presentation

There were 12 cases each of mild and severe head injury, while moderate head injury was found in nine. Among hyponatremic patients, there were four (33.33%) with mild, three with moderate (33.33%), and two (16.66%) with severe head injury.

Figure 3. Severity grading of TBI based on GCS

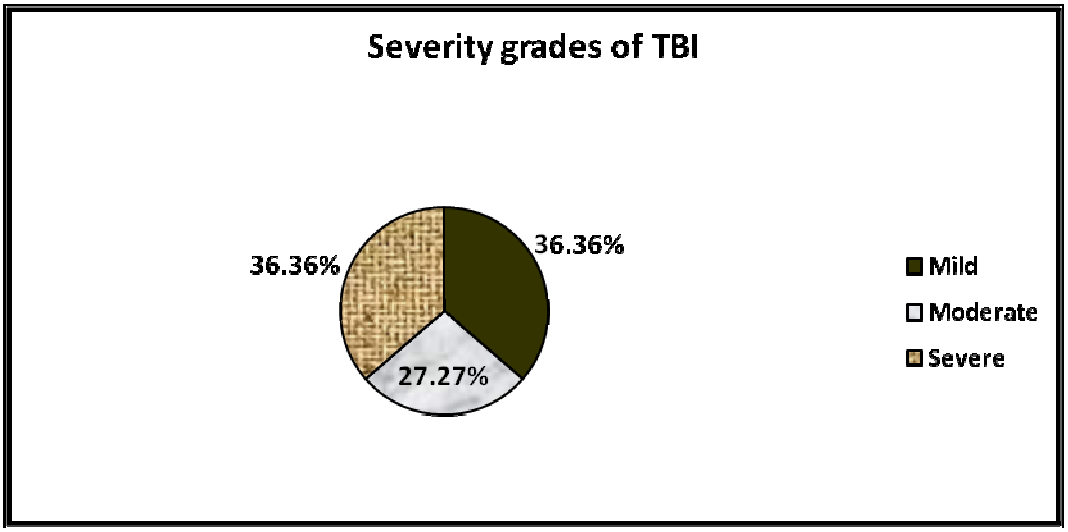
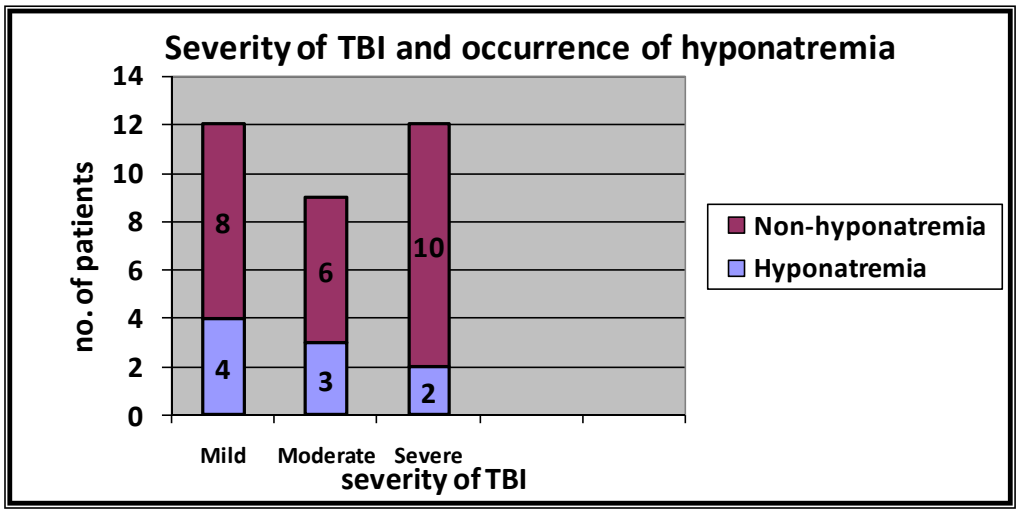


Figure 4. Proportional hyponatremic distribution among various TBI grades



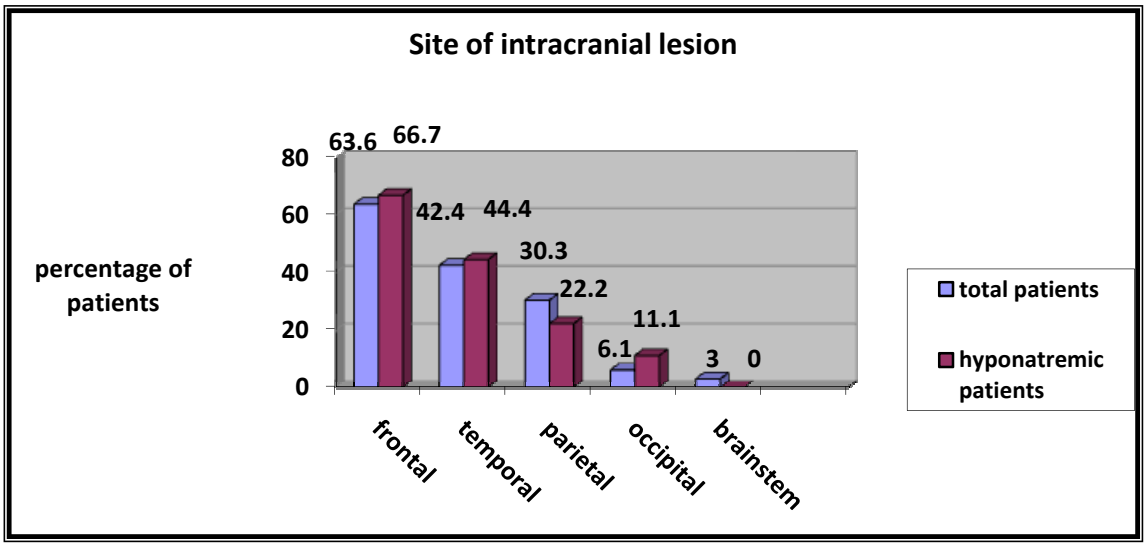
CT scan abnormality

None of the patients had a normal CT scan.

Site of intracranial lesion

Ten patients had lesion at more than one site. Frontal lesion in 21 patients was the most common, followed by temporal lesion in 14. One patient had a small hematoma in the brainstem. Among hyponatremic patients, three had lesion at more than one site. Frontal lesion was again the most common, followed by temporal lesion; six and four respectively.

Figure 5: Sites of intracranial lesion in total and hyponatremic patient population



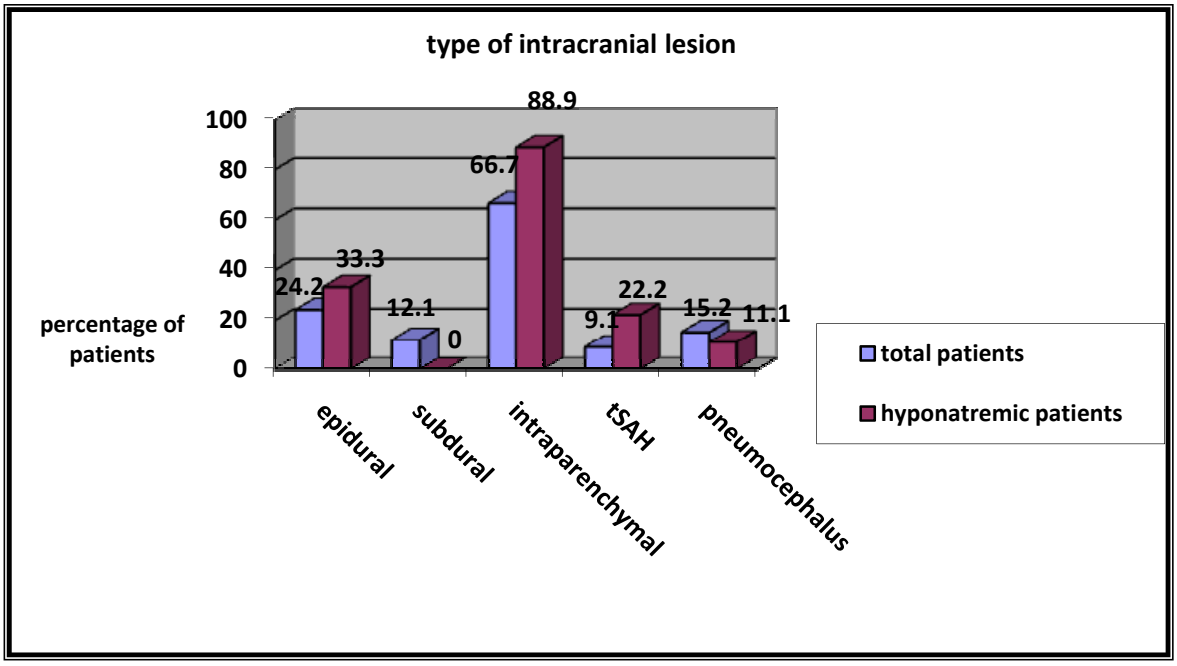
Type of intracranial lesion

Eight patients had an epidural lesion while four had a subdural lesion. There were total of 22 patients with intraparenchymal lesion but none of them had an intraventricular extension. Three patients also had pneumocephalus. Traumatic SAH was seen in five patients. Nine patients had more than one type of lesion.

Among the hyponatremic patients, intraparenchymal lesion seen in eight patients, was the most common lesion. None of the subdural lesions were associated with hyponatremia.

Epidural lesion, pneumocephalus and traumatic SAH was seen in three, two and one patients respectively. Three patients had more than one type of lesion.

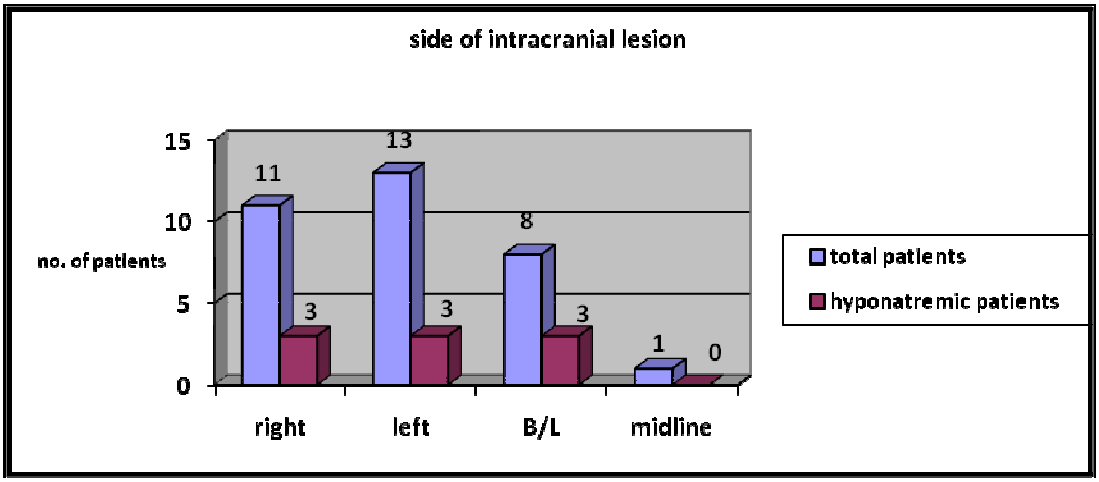
Figure 6. Type of intracranial lesion among total and hyponatremic patients



Side of intracranial lesions

Unilateral lesions predominated with 72.7% over bilateral lesions (24.2%). Left sided lesions (39.4%) were more common than the right ones. Among hyponatremic patients, unilateral, bilateral and midline lesions were observed in equal incidence, 33.33% each.

Figure7. Side of intracranial lesion among total and hyponatremic patients



CT scoring

Rotterdam CT grade

Most of the patients had Rotterdam scores two, three and four; 33.3, 24.2 and 27.3 % respectively. Hyponatremia was seen in scores two, three and four in increasing incidence, 22.2, 33.3, and 44.4% respectively (pearson correlation coefficient 0.983, p value 0.017; grades 1-4 considered for the analysis) (Table 1). No patients with score five however developed hyponatremia.

Figure 8 . Rotterdam CT grade among total and hyponatremic patients

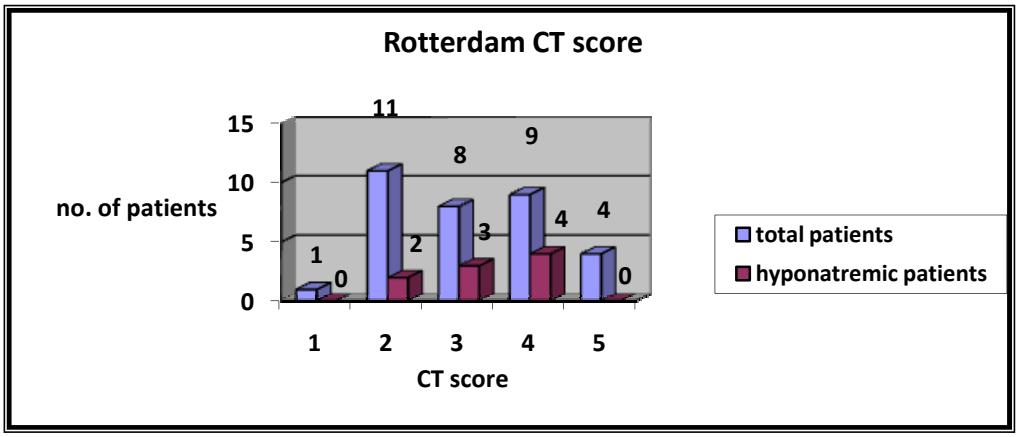


Table 1. Correlation of Rotterdam CT score and incidence of hyponatremia

		Rotterdam CT grade	Incidence of hyponatremia
Rotterdam CT grade	Pearson Correlation	1	.983(*)
	Sig. (2-tailed)	.	.017
	N	4	4
Incidence of hyponatremia	Pearson Correlation	.983(*)	1
	Sig. (2-tailed)	.017	.
	N	4	4

* Correlation is significant at the 0.05 level (2-tailed).

Surgical Intervention

19 (57.6%) patients had their hematoma surgically evacuated. Remainder 14 patients were conservatively managed.

Hyponatremia

Hyponatremia occurred in nine (27.27%) patients. Six of the patients had hyponatremia within the first week of injury. Clustering of cases was seen in late first week and early second week. Mean duration of hyponatremia was 1.78 (1-3) days with SD of 0.83. Minimum level of hyponatremia observed was 113 mEq/L. One other patient had hyponatremia down to 120 mEq/L. Rest of the seven patients had sodium levels above 125 mEq/L. All patients recovered well with oral salt supplementation and intravenous normal saline. One patient's sodium level dropped down to 113 mEq/L despite oral and intravenous supplementation, thus required fludrocortisone in addition. One other patient who went into hyponatremia 120 mEq/L on first post-operative day with frank picture of SIADH had to be kept on moderate fluid restriction. Two patients (22.2%) had recurrence of hyponatremia, at 11^{th} day in one and 12^{th} day in the other.

Figure 9. Timing of hyponatremia in TBI patients

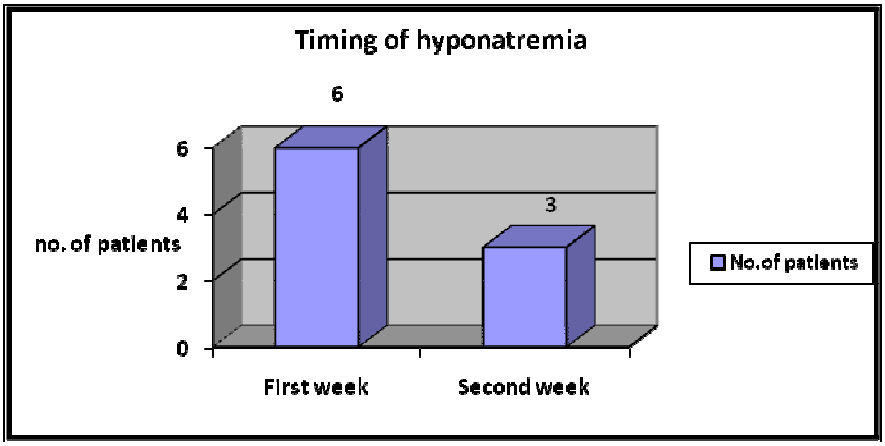


Table 2: Day of occurrence of hyponatremia

Day of occurrence of hyponatremia	No. of patients	Percentage
1	1	11.11%
3	1	11.11%
6	2	22.22%
7	2	22.22%
8	2	22.22%
9	1	11.11%

Figure 10. Timing of hyponatremia as from the day of admission

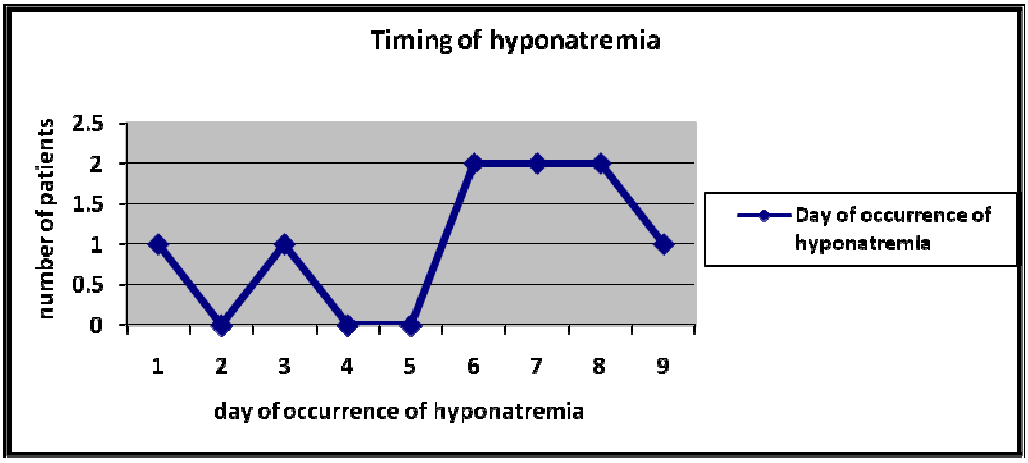
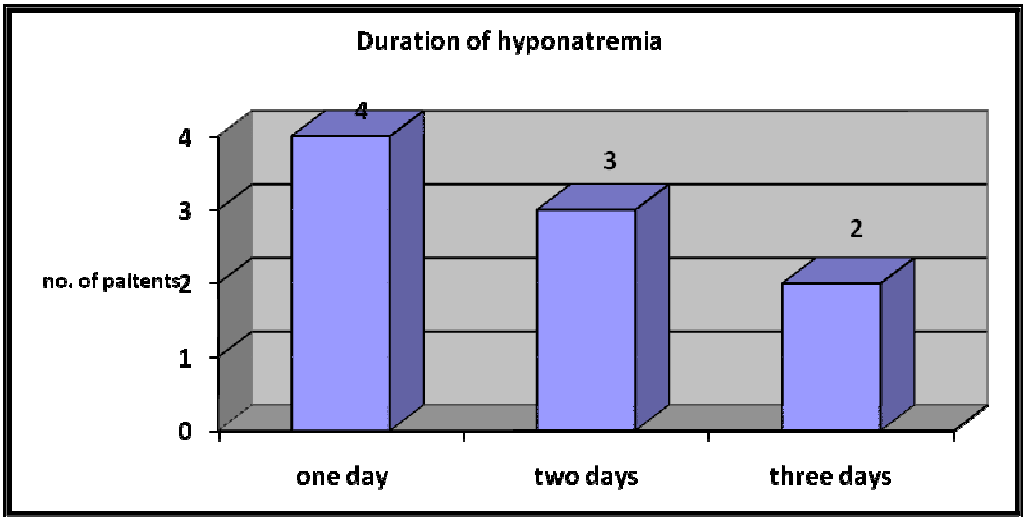


Figure 11. Duration of hyponatremia



Etiology of hyponatremia

Based on CVP measurement at the time of development of hyponatremia, etiology was ascertained. Five patients were diagnosed as cases of SIADH, while three as CSWS. As one of the patients didn't manifest any CVP variation, diagnosis could not be assigned.

Hyponatremia and Fractional Excretion of Uric Acid

Contrary to the expectation, FEUA as measured after detection of hyponatremia and after the correction of hyponatremia showed very bizarre findings.

Among five patients with SIADH consistent diagnosis, all had elevated FEUA at the first instance. In three, FEUA level decreased relative to previous level, but remained still elevated above the normal. In two, however, FEUA level further increased after correction of hyponatremia.

Among three patients with CSWS consistent diagnosis, one had normal FEUA at the beginning of hyponatremia. In all, however, FEUA remained persistently elevated compared to previous level.

In one of the hyponatremic patients however, CVP remained within normal range, making it difficult to assign a diagnosis. FEUA was elevated and remained persistently elevated even after correction of hyponatremia.

Table 3. CVP measurements, consistent diagnosis, and FEUA measurements among hyponatermic patients

Patient	CVP (Normal 6-10 cm)	Consistent diagnosis	Pre-FEUA (%)	Post-FEUA (%)
1	High/ 20 cm	SIADH	90.90	30.25
2	High/ 20 cm	SIADH	34.37	33.92
3	High/ 21 cm	SIADH	28.20	21.09
4	High/ 18 cm	SIADH	8.40	9.84
5	High/ 25 cm	SIADH	33.50	41.41
6	Normal/ 7 cm	-	12.39	17.42
7	Low/ 0 cm	CSWS	7.77	20.40
8	Low/ 3 cm	CSWS	11.25	29.72
9	Low/ 4 cm	CSWS	16.66	31.42

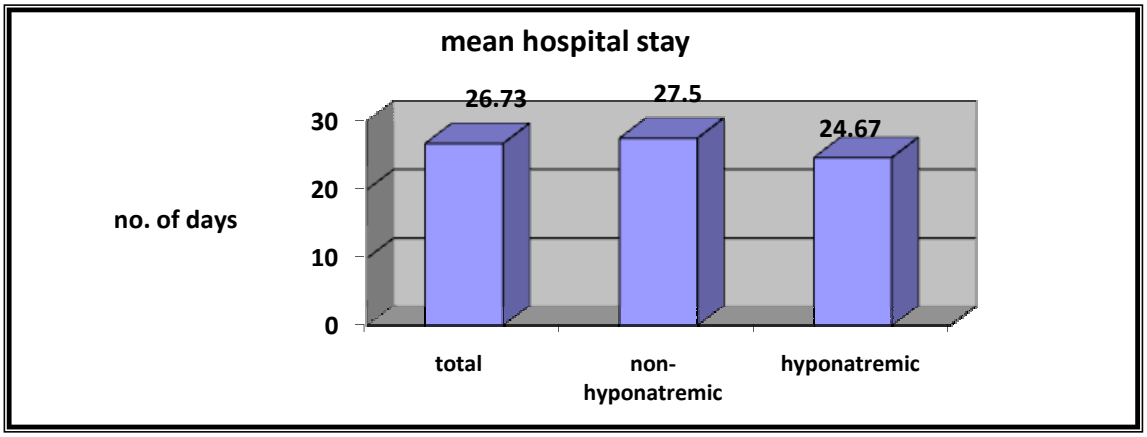
Variables associated with hyponatremia

Fisher's exact test was performed. Regarding the type, site and side of the lesion, GCS at the time of presentation, surgical intervention, and individual CT characteristics none of the variables were found to have significant association with the occurrence of hyponatremia.

Hospital stay

Overall mean hospital stay was 26.73 (7-90) days with SD 19.4. Among the hyponatremic patients, mean hospital stay was 24.67 (15-51) days with SD 13.4. No significant difference in means (p value 0.83) was shown by independent sample t-test (Table 2).

Figure 12. Mean hospital stay



Glasgow Outcome Score at discharge

Overall, mean GOS at discharge was 3 with SD 1.25. Among hyponatremic patients, mean GOS was 3.22 with SD 1.09. No significant difference in means (p value 0.553) was seen on independent sample t-test (Table 2).

Figure 13. Mean GOS of total and hyponatremic patients at discharge

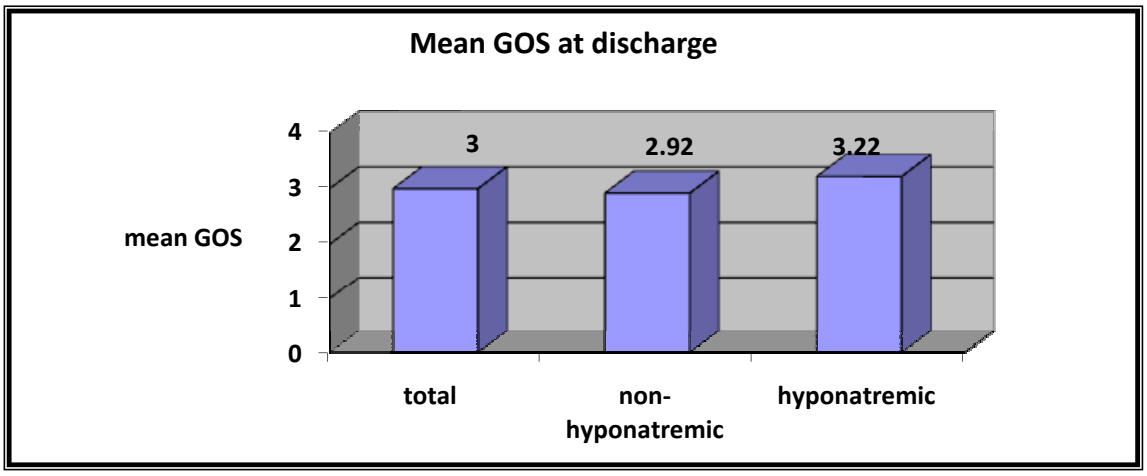


Table 4. T-test for the equality of means (duration of hospital stay and GOS at discharge)

	t-test for Equality of Means						
	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI of the Difference	
						Lower	Upper
Duration of hospital stay	-.217	31	.830	-1.62	7.459	-16.830	13.595
Glasgow Outcome at discharge	-.600	31	.553	-.29	.478	-1.262	.689

Discussion

Road traffic accident being the most common cause for traumatic brain injury, economically active age group and males are more afflicted, as seen in this study as well. Mean age and sex ratio of overall and hyponatremic patients are comparable.

Incidence of hyponatremia was 27.27%, which is comparable to that described by Mori et al among the subgroup of head injury patients who had intracranial bleeding.[8] Both mild and moderate head injuries had 33.33% hyponatremia, while with increasing severity, incidence dropped to 16.66%. Similar kind of observation were made by Doczi et al where hyponatremia was seen more in moderate head injury rather than severe.[38] Thus it seems that the occurrence of hyponatremia doesn't correlate well with GCS at admission. As seen in our study as well, 36.36% cases had mild head injury based on GCS score alone, while all of them had one or the other CT abnormality requiring intervention in many instances. There was no statistical correlation between GCS at initial presentation and occurrence of hyponatremia.

Interestingly however, observing the trend in Rotterdam CT scores, with increasing grades from two to four, incidence of hyponatremia also increased. Though there were no instances of hyponatremia in score five, the pattern seems convincing as to a CT grading might be a more important determinant of severity and hence occurrence of hyponatremia. With the exclusion of score five, where no hyponatremia was seen, a significant statistical correlation was also established.

Higher rate of surgical intervention was due to the inclusion of high risk trauma patients in the study; mild head injuries with normal CT scans were excluded. As most of the patients underwent surgical evacuation, grade five Marshall's CT grade would be the most common if classified accordingly. As the proportion of patients who underwent surgical intervention was proportionate among total and hyponatremic patients, here again it seems plausible that a CT scoring based on individual CT characteristics like that

of Rotterdam CT score would be more consistent with the severity and consequent events.[23]

Frontal location of the lesion was most common, be it among overall patients or hyponatremic patients. Similarly intraparenchymal lesion was of most common type. In contrary to the findings of Mori et al where chronic subdural lesion were associated with 15.9% hyponatremia, none of the acute subdural lesions in our series had hyponatremia. [8] Side of the lesion, right, left or bilateral, were all associated with equal incidence of hyponatremia.

Since the policy of our institution is to avoid fluid restriction in patients with head injury, irrespective of the diagnosis, all patients are treated with oral salt supplementation and intravenous normal saline after hyponatremia is observed. Hyponatremia corrected in almost all instance with this treatment strategy, probably because most of the cases were only mild. In one instance, patient went into frank SIADH on first post-operative day with significantly decreased urine output. The following day, patient had an excess of urine output leading to spontaneous correction of hyponatremia and never recurred again. This particular instance suggests that over-zealous attempt at correction might lead to too rapid a correction of hyponatremia, which should always be avoided.

Two-thirds of hyponatremic cases occurred during the first week. This was noticed in days first, third, sixth, and seventh, in contrary to what was described by Mori et al.[8] He described a peak of hyponatremia in first week within first three days. In our finding, clustering of cases was seen in late first week and early second week.

Given a typical case scenario, differentiation of SIADH and CSWS might not sound difficult. Yet, at clinical practice confusion still persists. In trying to solve this confusion, Maesaka et al [19] had suggested that FEUA increases in both conditions at the onset of hyponatremia while after correction, it persists at higher level in CSWS and normalizes in SIADH. In this study, FEUA was measured in all cases who developed hyponatremia

both prior and after the correction of hyponatremia. Contrary to the presumed findings, FEUA measurement failed to display consistent findings.

Mean hospital stay and mean GOS at discharge was comparable among overall, hyponatremic and non-hyponatremic patients. There was no significant difference of means for both variables, suggesting that with prompt identification and appropriate treatment, hyponatremia does not confer any additional morbidity.

Conclusion and Recommendations

Hyponatremia is common in traumatic brain injury, with an incidence of 27.27% among high risk patients. Most of them can be attributed to SIADH, though CSWS also occurs in a few. CT scoring of injury has better correlation to its occurrence rather than initial GCS. With prompt identification and treatment, hyponatremia doesn't result in prolonged hospital stay or any undue morbidity and mortality. Measurement of FEUA doesn't appear consistent enough for the differentiation of SIADH or CSWS.

As this study has its limitation in terms of small population, further studies will be necessary to build on the findings generated by this study.

Since early identification of hyponatremia allows prompt treatment and avoid undue prolongation of morbidity, it seems plausible that daily sodium level measurement at least for initial ten days should be routinely done especially in high risk traumatic brain injuries.

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Proforma

Case no: **IP no:**

Date of admission: **Date of discharge:**

Name: **Age/ Sex:**

GCS at the time of presentation:

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

History of loss of consciousness:

None < 5 mins > 5 mins

History of amnesia/ transient impairment of memory: Y/ N

CT characteristics:

Dimension of the lesion: …… Volume:……..

Location of the lesion: F T P O …….

Midline shift: normal <5 mm >5 mm

Basal cisterns: normal compressed obliterated

Type of mass lesion:

epidural

subdural

intraparenchymal without intraventricular extension

intraparenchymal with intraventricular extension

tSAH

Associated chronic co-morbidity:

1. DM
2. HTN
3. Renal disease
4. Others

Baseline Investigation (U/Cr/Glucose): normal abnormal

Daily sodium monitoring:

Day	CVP	Na/K	Remarks(symptom status/ other investigations)
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			

Diagnosis consistent with:

1. SIADH
2. CSWS
3. Others……

Hyponatremia normalized in :……..days

Basic treatment principle:

1. fluid restriction
2. oral salt
3. isotonic saline
4. hypertonic saline
6. volume expanders
5. loop diuretics
7. blood transfusion
8. demeclocycline
9. hydrocortisone

Status after correction of hyponatremia:

1. symptomatically improved and no recurrence
2. symptomatically improved followed by recurrence
3. development of complications consistent with ODS(quadriplegia, pseudobulbar palsy, seizures, coma, death.)

Glasgow outcome at discharge: 1 2 3 4 5