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The use of electrolyte-free water clearance, sodium clearance and urine potassium to urine sodium ratio to distinguish between the syndrome of inappropriate antidiuretic hormone release and cerebral salt wasting syndrome in hyponatraemic patients in a neurosurgical intensive care unit

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The use of electrolyte-free water clearance, sodium clearance and urine potassium to urine sodium ratio to distinguish between the Syndrome of Inappropriate Antidiuretic Hormone Release and Cerebral Salt Wasting Syndrome in hyponatraemic patients in a Neurosurgical Intensive Care Unit.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa in partial fulfilment of the requirement for the degree of Master of Medicine in the Department of Neurosurgery.

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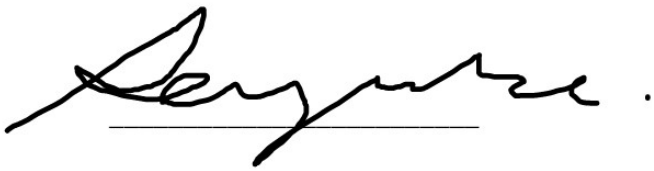
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DECLARATION.

I, Victor Magumbeze, declare that this research report is my own work, in design and execution. It is being submitted for the degree of Master of Medicine (Neurosurgery), University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at this or any other University**.**



Signature

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ABSTRACT.

Aim

Deciding the cause of hyponatraemia from physical examination of a patient and laboratory investigations of serum and urine biochemistry is often not possible. The reasons lie in the facts that physical examination cannot accurately define a patient's extracellular fluid volume and laboratory investigations do not provide clear discrimination between different causes of hyponatraemia. The aim of this study is to determine whether or not calculation of the modified electrolyte-free water clearance (MEFWC), sodium clearance (CNa) and the urine potassium to urine sodium ratio (UK/UNA ratio) will provide enough additional evidence to enable a clinician to make an accurate distinction between the syndrome of inappropriate anti-diuretic hormone release (SIADH) and the cerebral salt wasting syndrome (CSWS).

Method

Urine samples, collected over a period of 1 hour from hyponatraemic patients in a neurosurgical intensive care unit, were analyzed for sodium and potassium concentrations. This information was used to calculate values for MEFWC, CNa and UK/UNa ratio. Patients were divided firstly into two primary groups on the basis of whether MEFWC value was positive (Group P) or negative (Group N). Each of the primary groups was then divided into three sub-groups based on whether CNa value was less than normal (sub-groups P1 and N1), normal (sub-groups P2 and N2) or greater than normal (sub-groups P3 and N3). Lastly, UK/UNa ratio was calculated for each patient in the study.

Results

A total of 32 patients entered the study. There were 13 patients in Group P and 19 patients in Group N. Further sub-division was such that sub-groups P1, P2 and P3 consisted of 4, 5 and 4 patients, respectively. Sub-groups N1, N2 and N3 consisted of 0, 9 and 10 patients respectively. The MEFWC for sub-group N2 was -8.87 ± 7.58 millilitres/ hour (ml/ hr) and that for sub-group N3 was -51.48 ± 32.30 ml/ hr. The CNa for these two groups were 58.28 ± 18.47 ml/ hr and 179.88 ± 86.64 ml/ hr, respectively. The UK/UNa ratio was found to be 0.31 ± 0.12 for sub-group N2 and 0.22 ± 0.15 for sub-group N3. Although the differences in MEFWC are not statistically significant

the values for CNa are statistically different. By definition, patients with hyponatraemia and negative MEFWC are suffering from the SIADH. UK/UNA ratio of less than unity indicates that neither group has hypovolaemia. The different CNa indicate that patients with SIADH may have different levels of total body sodium (TBNa) and, therefore, different sodium excretion rates.

By definition, patients with positive MEFWC do not have SIADH. Patients in sub-groups P1, P2 and P3 all exhibited positive MEFWC (18.0 ± 9.89 ml/ hr, 49.65 ± 46.08 ml/ hr and 60.28 ± 58.75 ml/ hr, respectively). The differences in MEFWC between the P sub-groups are not statistically significant but do indicate that there is a wide range of total body water (TBH_2O) in Group P patients. The CNa values for sub-group P1 (11.69 ± 3.10 ml/ hr), P2 (51.74 ± 19.55 ml/ hr) and P3 (195.17 ± 98.32 ml/ hr) are statistically significantly different. These results indicate that there is a wide variation in TBNa in Group P patients.

Only sub-group P1 has UK/UNa ratio value greater than unity (1.95 ± 0.91). Thus, sub-group P1 is the only sub-group containing patients that can be classed as having hypovolaemia. It is also the sub-group with the lowest CNa. Sub-groups P2 and P3 do not have hypovolaemia as indicated by UK/UNa ratios less than unity (0.49 ± 0.24 and 0.29 ± 0.11, respectively).

Conclusion

The study demonstrated that calculation of the three indices, MEFWC, CNa and UK/UNa ratio provided enough information to readily identify patients with SIADH – on the basis of negative MEFWC, normal or increased CNa and an absence of hypovolaemia.

The study was able to identify patients with positive MEFWC, normal or increased CNa and absence of hypovolaemia indicating that various combinations of increased TBH_2O and increased TBNa were responsible for the hyponatraemic condition in these patients.

A sub-group of patients with positive MEFWC, a low CNa and hypovolaemia was identified - patients who are retaining sodium and water to repair a deficit in TBNa and TBH_2O.

The study did not identify any patients with hypovolaemia co-existing with a normal or an increased CNa which could be compatible with a diagnosis of CSWS.

ABBREVIATIONS.

ADH: Antidiuretic hormone.

ANOVA: Analysis of Variance.

CH_2O: free water clearance.

C^eH_2O: electrolyte-free water clearance.

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CNa: sodium clearance.

Cosm: osmolar clearance

CSWS: Cerebral Salt Wasting Syndrome.

CVP: central venous pressure.

FENa: fractional excretion of sodium

ICU: Intensive Care Unit.

l/ 24 hr: litres/ 24 hours

MEFWC: modified electrolyte-free water clearance.

ml/ hr: millilitres/ hour

mmol/ ml: millimoles/ millilitre.

mOsm/ kg: milliosmoles/ kilogram water.

NSICU: Neurosurgical Intensive Care Unit.

SD: standard deviation.

SIADH: Syndrome of Inappropriate Anti Diuretic Hormone Release.

SNa: serum sodium.

SK: serum potassium.

Sosm: serum osmolality.

TBH_2O: total body water.

TBNa; total body sodium.

UNa: urine sodium concentration.

Uosm: urine osmolality.

UK: urine potassium.

V: urine volume.

$\mathcal{V}$: urine flow rate (volume/ unit time).

1. INTRODUCTION.

The presence of hyponatremia in any patient evokes concern. Hyponatraemia may occur in conjunction with a hypo-, hyper-, or iso-osmolar state. When it occurs together with hypo-osmolality it indicates that the total body sodium (TBNa) to total body water (TBH_2O) ratio has been disturbed.

A decrease in serum osmolality (Sosm) is of clinical importance because of the effect exerted on cell volume. Water is able to cross cell membranes and expand cell volume. This will adversely affect cellular function of the brain and other organ systems. Consequently, the appearance of hyponatremia in any person requires rapid diagnosis of cause followed by appropriate treatment.

Hyponatremia is a common electrolyte abnormality in the Neurosurgical Intensive Care Unit (NSICU) and is usually defined as a serum sodium (SNa) of less than 135 millimoles/ litre (mmol/ l)[1]. It is often classified as mild, moderate or severe depending on the serum level[2].

Causes of hyponatremia in NSICU include the Syndrome of Inappropriate Anti-Diuretic Hormone Release (SIADH), Cerebral Salt Wasting Syndrome (CSWS), inappropriate fluid administration and diuretic drugs, to name only a few.

Determining the cause of hyponatraemia solely from laboratory investigations is difficult because there is a wide range and considerable overlap of the serum and urine laboratory values quoted for different causes of hyponatraemia. An example of this is found with SIADH and CSWS. The range of values for urine electrolyte and urine osmolality (Uosm) is similar in these two conditions. In addition, many authorities maintain that CSWS cannot be diagnosed on serum and urine biochemistry alone. Only when expected biochemical disturbances exist together with hypovolaemia in the patient under investigation can a diagnosis of CSWS be made[3].

Since several texts indicate that SIADH and CSWS are indistinguishable biochemically and since a number of opinions dispute the existence of CSWS[4, 5] there is a need for investigations that could shed light on these specific issues.

The purpose of this research project is to calculate values for clearance of electrolyte-free water, sodium clearance (CNa) and, in order to have a marker for hypovolaemia, the urine potassium (UK) to urine sodium (UNa) ratio from timed collections of urine in NSICU patients who have hyponatraemia. It is hoped that the information gathered will enable clinicians to make a reliable diagnosis of the cause of hyponatraemia, distinguish between SIADH and CSWS and provide the appropriate therapy to each patient.

2 LITERATURE REVIEW.

2.1 Definition of Hyponatraemia.

SNa describes the ratio of TBNa to total body water TBH_2O but explains nothing about the finite value of each substance. A decreased SNa only indicates that, compared to TBNa, there is a relative increase in TBH_2O irrespective of the actual TBNa at the time of measurement.

Hyponatraemia may be associated with low, normal or increased Sosm. The term "pseudo-hyponatraemia" describes those situations where hyponatraemia co-exists with a normal or increased Sosm. The term signifies that such conditions are due to an accumulation of a non-sodium osmotic substance in the blood.

Hyponatraemia, when the word is used in a descriptive sense, is usually defined as a SNa of less than 135 millimoles/ litre (mmol/ l)[1].

Hyponatraemia that is associated with low Sosm is referred to as "true hyponatraemia" or "hypotonic hyponatraemia" and, in this instance, is defined as SNa less than 135 millimoles/ millilitre (mmol/ l) that is associated with Sosm of less than 280 milliOsmoles/ kilogram (mOsm/ kg)[6].

2.2 Epidemiology.

Gill and Leese[2] state that hyponatraemia "…….is one of the most common biochemical abnormalities encountered in clinical practice". The frequency described by various studies is determined both by serum value and the population group being investigated[2,7]. Amongst neurosurgical patients, hyponatremia is found in 15% to 20% of those with traumatic brain injury, more than 50% of those with subarachnoid hemorrhage and between 10 to 20% of patients' with intracranial tumours and hematomata[8].

2.3 Manifestations and effects of hyponatremia.

Hyponatremia has the potential to cause serious damage to the neurosurgical patient. The condition may present with symptoms that mimic a neurologic disorder or may exacerbate pre-existing neurological dysfunction. Hyponatremia associated with hypotonicity causes an increase in intracellular fluid volume which may lead to cerebral oedema, may increase intra-cranial pressure and so worsen neurological outcome[9].

Due to slow compensatory mechanisms in the brain, acute hyponatremia is poorly tolerated. Symptoms of mild hyponatremia include anorexia, headache, and changes in mental concentration, irritability, dysgeusia and muscle weakness. Severe hyponatremia (SNa less than 125 mmol/ l) or a rapid drop (more than 0.5 mmol/ hr) of SNa can cause neuromuscular excitability, cerebral oedema, muscle twitching and cramps, nausea, vomiting, confusion, seizures, respiratory arrest and may lead to permanent neurologic injury, coma or death[10].

2.4 SIADH.

SIADH is a clinical condition, first described by Schwartz et al[11], in which Antidiuretic Hormone (ADH) or an ADH-analogue is released into circulation in the absence of an osmolality-dependent or volume-dependent physiologic stimulus. Release of the hormone or its analogue may be a drug-related or a disease-related phenomenon and the source may be the pituitary gland or an ectopic site.

The consequence of the disturbance is impaired renal water excretion which leads to hyponatraemia and serum hypo-osmolality[12].

Diagnostic criteria for SIADH have been proposed by various well respected authorities[1, 13, 14, 15]. Although the suggestions for clinical findings are consistent and accepted, there are differences in the laboratory cut-off ranges in the various proposals. In general, the commonly suggested criteria are as follows:

- Clinical signs suggesting a normal extracellular fluid volume,
- Absence of hypothyroidism,
- Absence of hypocortisolism,
- Presence of hyponatraemia,
- Decreased Sosm,
- Increased UNa,
- Uosm greater than or equal to 100 mOsm/ kg.

Over time various clinical or laboratory markers, for example: serum uric acid levels[16] have been suggested as useful additions to aid or enable confirmation of diagnosis of SIADH. None of the new suggestions have provided a better aid to diagnosis of the syndrome than the criteria listed above.

A simplified description of SIADH is that it is a condition associated with fluid retention, hyponatraemia, serum hypo-osmolality, natriuresis and urine that is not maximally dilute.

2.5 CSWS.

In 1950 Peters and co-workers[17] reported on "a salt-wasting syndrome associated with cerebral disease". However, it was not until 1954 that Cort[18] in his description of a patient similar to those reported by Peters *et al*[17], first used the phrase "cerebral salt wasting".

Since the original description of the syndrome, academic literature has not been able to agree on a uniform definition for CSWS nor on the exact clinical and biochemical disturbances that would enable a clinician to identify the condition consistently and accurately. More importantly, various authorities have cast doubt on the existence of CSWS[2, 4, 5] while others support the recognition of the condition[19, 20, 21, 22].

In the absence of an agreed definition it is best to say that CSWS is considered to be a cause of hyponatraemia in patients with intracranial pathology. It is thought to result from an abnormal increase in sodium excretion via the kidney. Consequently, it is associated with an elevated UNa and with depletion of the extracellular fluid volume.

Criteria suggested for the diagnosis of CSWS are:

- Clinical signs indicating a decreased extracellular fluid volume,
- Presence of hyponatraemia,
- Decreased Sosm,
- Increased UNa,
- Uosm greater than or equal to 100 mOsm/ kg.

A simple description of CSWS is that it is a condition associated with evidence of hypovolaemia, hyponatraemia, serum hypo-osmolality, natriuresis and urine that is not maximally dilute.

The pathophysiology of CSWS is not known. Two hypotheses have been proposed:

a) Release of a humoral agent from the brain: the suggestion is that a natriuretic hormone is released from the brain which stimulates sodium loss and leads to hypovolaemia. The stimulus for release of the humoral factor is unknown. Various causative substances have been proposed: atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide and dendroaspis natriuretic peptide[23]. Whether these peptides act independently or in concert has not been discussed.

b) Adrenergic hormone induced pressure natriuresis: a “pressure natriuresis” is a situation whereby sodium loss from the kidney is proportional to the prevailing arterial blood pressure. Blood levels of adrenergic hormones are elevated when brain injuries occur and may remain elevated or surge during clinical care. An associated increase in arterial blood pressure due to sympathetic nervous system stimulation could lead to the phenomenon of pressure natriuresis[5].

At the present time these suggestions remain hypotheses.

2.6 Differentiating between SIADH and CSWS.

Based on current knowledge of SIADH and CSWS, it is not possible to differentiate between the two conditions on biochemical information alone. For example: concerning UNa, Rahman *et al*[1] suggest that in a hyponatraemic patient both SIADH and CSWS should be considered if UNa is more than 25 mmol/l. Yee *et al*[24] and Suggala *et al*[25] indicate that the lower limit for UNa in both conditions is greater than 40 milliequivalents/ litre (sic). Other authors simply state that SIADH has a “high” UNa and CSWS has a UNa that is “very high”[26]. Of considerable importance are the observations by Musch and Decaux[27] that UNa in SIADH is a reflection of sodium intake and although UNa in SIADH is not usually low it may be if salt intake has been low.

There is general agreement that both SIADH and CSWS display a natriuresis. In SIADH the natriuresis is due to removal of water from urine thereby increasing the final concentration of sodium in urine[13]. In CSWS, natriuresis is due to increased excretion of sodium via the kidney[3]. However, inspection of the UNa value does not provide the clue as to which of the two processes is operating in an individual patient.

Those authorities that recognise the existence of CSWS indicate that it is essential to distinguish CSWS from SIADH because the treatment of the two conditions is completely different[20, 21, 23, 25]. CSWS requires replacement of sodium and intravascular volume while SIADH requires fluid restriction and seldom requires sodium replacement except when a patient exhibits symptomatic hyponatraemia. Failure to apply the correct treatment may result in serious consequences for the patient.

Supporters of existence of CSWS agree that the cardinal sign that permits recognition of CSWS, and distinguishes it from SIADH, is the presence of hypovolaemia[3, 7, 19]. When hypovolaemia is present

together with the appropriate biochemical disturbance then the diagnosis is clear. SIADH, on the other hand, is recognised by the presence of euvolaemia and appropriate biochemical disturbances.

In effect, because the biochemical disturbances are not different in the two conditions, the diagnosis rests entirely on a clinician's assessment of a patient's extracellular fluid volume. This requirement raises a new problem. There is evidence that a clinician's ability to correctly predict, from a physical examination alone, a patient's extracellular fluid volume status is associated with almost a 1 in 2 chance of making an incorrect assessment[28]. Even in situations where invasive monitoring is used to determine intravascular volume status, it may still be difficult to come to a reliable conclusion[29, 30].

2.7 The importance of identifying the cause of hyponatraemia.

Hyponatraemia has many causes. SIADH and CSWS represent only two examples. The clinical situation in which hyponatraemia occurs is as relevant as the severity of the presentation. Urgency of treatment is guided by the presence or absence of symptoms. In the neurosurgical patient, timeous diagnosis of hyponatremia is considered to be of utmost importance[10]. However, in any patient, determination of the cause is essential because the aetiology determines the treatment approach — which differs according to cause, severity and urgency.

2.8 Free Water Clearance.

In 1952 an American physiologist, H. W. Smith[31], suggested that urine could be viewed as two separate components. One component contained the solute being removed by the kidney, the other consisted of solute-free water which the kidney would either excrete or retain. The volume of urine containing solute represents the volume of serum that is cleared of solute per unit time and is called "osmolar clearance" (Cosm). The volume of solute-free water represents the amount of serum from which water is either removed or retained per unit time and is called the "free water clearance" (CH_2O). Since osmolar clearance can be calculated from knowledge of Sosm, Uosm and urine flow rate ($\mathcal{V}$), the volume of CH_2O could be determined as follows:

$$\mathcal{V} = \text{Cosm} + \text{CH2O}$$

Where:

$\mathcal{V}$ = urine flow rate (volume/ unit time), Cosm = volume of plasma cleared of solute/ unit time, and CH_2O = volume of free water excreted or retained/ unit time.

Since Cosm may be calculated from:

$$\text{Cosm} = \frac{\mathcal{V} \text{ x Uosm}}{\text{Sosm}}$$

Then:

$$CH_2O = \mathcal{V} - \left(\frac{\mathcal{V} \text{ x Uosm}}{\text{Sosm}}\right)$$

This simplifies to:

$$CH_2O = \mathcal{V}\left[1 - \left(\frac{\text{Uosm}}{\text{Sosm}}\right)\right]$$

Where: Uosm and Sosm are measured in milliosmoles/ kilogram water (mOsm/ kg)

By convention, excretion of free water by the kidney is designated “positive free water clearance” and retention of water is designated “negative free water clearance”. Since free water clearance describes whether the kidney is excreting or retaining water it provides clinicians with a means to characterize both normal and abnormal water homeostasis in patients. In the presence of normonatraemia, positive free water clearance suggests that an excess of TBH_2O is being removed and negative free water clearance suggests that a TBH_2O deficit is being repaired. In the presence of hyponatraemia, negative free water clearance is an abnormal finding and indicates that the ADH-renal axis response is dysfunctional[32]. Positive free water clearance in the presence of hypervolaemic or euvolaemic hyponatraemia suggests the appropriate removal of an excess of TBH_2O or that an attempt to normalize TBNa to TBH_2O ratio is in progress. Positive free water clearance is also found in the presence of hypovolaemic hyponatraemia. In this situation, despite the presence of hypovolaemia, the water loss is a consequence of an obligatory requirement to provide solvent for the removal of urea[32].

In 1981, Goldberg[33] reviewed the concept of free water clearance. He explained that urea is a major determinant of Uosm but it is a minor determinant of Sosm. Thus “free water” was not “pure water”

since it contained urea. The important determinants of Sosm are the sodium and potassium salts in the extracellular fluid compartment. The major determinants of Uosm are the sodium salts, potassium salts and urea present in urine. Goldberg[33] argued that it was more important for the clinician to know the volume of electrolyte-free water than the volume of urea-containing free water. Consequently, he proposed that clinicians need only be concerned with water balances that are determined by the electrolytes present in serum and urine. Free water clearance should be renamed "electrolyte-free water clearance" (C^eH_2O) and the equation rewritten as follows:

$$C^eH_2O = \mathcal{V}\left[1 - \left[\frac{(UNa+UK)}{SNa}\right]\right]$$

Where: $\mathcal{V}$ = urine flow rate (volume/ unit time). CeH2O has units of volume/ unit time. UNa, UK and SNa are measured in millimoles/ litre (mmol/ l).

C^eH_2O, like CH_2O, may have a positive or a negative value.

Nguyen and Kurtz[34] have further reviewed physiological determinates of sodium concentrations in extracellular fluid. In their theoretical analysis[34], they proposed the Modified Electrolyte-Free Water Clearance (MEFWC) Equation as follows;

$$MEFWC = \mathcal{V}\left[1 - \left[\frac{\{1.03(UNa+UK)\}}{(SNa+23.8)}\right]\right]$$

Where: $\mathcal{V}$ = urine flow rate (volume/ unit time). MEFWC has units of volume/ unit time. UNa, UK and SNa are measured in mmol/ l.

MEFWC may have a positive or a negative value.

The proposed equation has gained acceptance as an accurate measure of the clearance of free water following a clinical evaluation by Lindner and Schwartz[35].

2.9 Sodium Clearance

Sodium clearance (CNa) describes the volume of serum from which sodium is removed by the kidney per unit time. Shoker[32] suggested this index, noting that CNa is calculated from the CNa Clearance Equation, detailed below:

$$\text{CNa} = \frac{\mathcal{V}(\text{UNa x 2})}{(\text{SNa x 2})}$$

Where $\mathcal{V}$ = urine flow rate (volume/ unit time). CNa has units of volume/ unit time. UNa and SNa are measured in mmol/ l.

CNa is a measure of the renal response to changes in TBNa and to changes in effective circulating volume. Thus CNa will be increased when TBNa is increased and low when TBNa is low. CNa will also have a low value when effective circulating volume is low or becomes ineffective. Shoker[32] has provided a detailed analysis of the clinical interpretation of this index noting that the normal range for CNa is 0.60 - 2.24 litres/ 24 hours (l/ 24hr), equivalent to 25 – 93.3 millilitres/ hour (ml/ hr). Furthermore, Shoker has established that any value greater than or equal to 0.2 l/ 24hr (8.3 ml/ hr) indicates that sodium is being lost from the body via a renal process while a value of 0.1 l/ 24hr (4.1 ml/ hr) or less indicates loss of sodium via an extra-renal process.

2.10 Urine potassium to urine sodium ratio.

As alluded to earlier, it is difficult for a clinician to make an accurate assessment of a person's extracellular volume, even with sophisticated measurement techniques[28, 29, 30]. Cogan[36] noted that the ratio of urine potassium to urine sodium (UK/UNa ratio) reflects serum aldosterone concentration. He pointed out that a ratio equal to or exceeding unity suggests either primary hyperaldosteronism or a state of extracellular volume contraction. Thus, this ratio could provide a method of identifying a decreased extracellular volume or comparing the state of the extracellular volume of different groups of patients. It seems that the UK/UNa ratio has received neither clinical attention nor investigation. However, urine potassium to urine potassium plus urine sodium ratio has been investigated in children with nephrotic syndrome and was found to correlate both with an increase in serum aldosterone level[37] and with a decrease in glomerular filtration rate[38] that was associated with hypovolemia.

The UK/UNa ratio is calculated as follows:

$$\text{UK/UNa ratio} = \frac{\text{UK}}{\text{UNa}}$$

Where; UK and UNa are measured in mmol/ l.

3. RATIONALE FOR THE STUDY

Making a timely and accurate diagnosis of the cause of hyponatremia is important in both the acute and chronic settings. Although there are many causes of hyponatraemia, differentiating between SIADH and CSWS is particularly important as SIADH is treated by fluid restriction while CSWS is treated by sodium and water replacement[39]. Since these two treatment strategies are direct opposites, misdiagnosis or failure to distinguish between these two conditions may have significant consequences for the critically ill neurosurgical patient.

If it is not possible to distinguish correctly SIADH from CSWS using physical examination and biochemical information, then another method or combination of methods must be found in order to achieve the distinction.

4. AIM OF THE RESEARCH.

The aim of the project is to determine whether calculation of MEFWC, CNa and UK/UNa ratio will provide enough information:

a) to identify the physiological disturbance leading to hyponatraemia, and
b) to differentiate between SIADH and CSWS

in a group of hyponatraemic patients in NSICU.

5. HYPOTHESIS.

The hypotheses for the research project are:

a) that, in a group of hyponatraemic patients, calculations of MEFWC, CNa and UK/UNa ratio will enable the clinician to distinguish between the conditions of SIADH and CSWS.
b) that SIADH will be recognized by a negative value for MEFWC, a value of less than 1 for UK/UNa ratio and CNa values that may range from low or normal to high.
c) that CSWS will be recognized by a UK/UNa ratio greater than 1 and CNa values that, in the presence of hyponatraemia, suggest an inappropriately high renal sodium excretion rate.

6. OBJECTIVES OF THE RESEARCH.

The objectives of the project are as follows:

a) To identify, on the basis of the routine daily blood sample, those patients in the NSICU who are hyponatraemic.

b) To obtain a one-hour timed collection of urine from each patient identified as having hyponatraemia.

c) To obtain, via the hospital laboratory service, the urine sodium and potassium concentrations and the urine osmolality value for each urine sample.

d) To calculate MEFWC, CNa and UK/UNa ratio for each patient from the respective serum and urine sample results.

c) To identify from the calculations whether a patient has SIADH or CSWS.

7. PATIENTS AND METHODS.

Patients with hypotonic hyponatraemia who were receiving clinical care in a NSICU and met the inclusion criteria were entered into the study. Inclusion criteria were as follows:

a) in receipt of clinical care in NSICU,
b) age 18 years or over,
c) SNa less than 135 mmol/ l
d) UNa greater than or equal to 20 mmol/ l
e) Measured Sosm less than 285 mOsm/ kg
f) Blood glucose less than 8.1 mmol/ l
g) Serum urea less than 7.1 mmol/ l
h) No exposure to mannitol, diuretic drugs, inotropic drugs, steroid drugs or aminoglycoside drugs prior to recruitment
i) No evidence of renal dysfunction, adrenal disease, thyroid disease or cardiac failure.
j) No evidence of hyperproteinaemia or hyperlipidaemia.

For the purposes of the study, eligible patients recognized to have hyponatraemia on routine daily laboratory blood analysis were managed as follows:

a) A timed 1-hour urine sample was collected and, after noting the urine volume, an aliquot was delivered to the hospital laboratory service for determination of osmolality and sodium and potassium concentrations.
b) A venous blood sample was drawn and delivered to the hospital laboratory service for determination of Sosm.

Serum and urine samples were analyzed by the hospital laboratory service. Results were available on a same-day basis. Electrolytes were measured using the Indirect Ion-Selective Electrode technique housed in a Roche/ Hitachi Cobas-8000 Analyzer® (Roche Diagnostics, Indianapolis, United States of American). An Advanced® Micro-Osmometer Model 3320 device (Advanced Instruments, Massachusetts, United States of America), utilizing the depression of freezing point method, was used to measure osmolality. The 1-standard deviation imprecision of this device is ± 2 mOsm/ kg.

When the laboratory results were known MEFWC, CNa and UK/UNa ratio were calculated from the MEFWC Equation, the CNa Equation and by dividing UK by UNa, respectively. Laboratory and calculation results were immediately made available to the treating clinician so that patient management continued uninterrupted by the study. Patient clinical care was not undertaken by the study investigator.

Once calculations were completed the patients were divided into 2 groups on the basis of the MEFWC value. Group N comprised those patients with negative MEFWC and Group P those patients with positive MEFWC. Group N was then further divided into three sub-groups on the basis of the CNa value. Sub-group N1 consisted of patients with CNa value of 8.3 – 24.9 ml/ hr. Sub-group N2 consisted of those patients with CNa value 25 – 93.3 ml/ hr and Sub-group N3 those with a CNa value greater than or equal to 93.4 ml/ hr. Group P was similarly divided into three sub-groups - P1, P2 and P3 - using the same value ranges for CNa, respectively.

8. ETHICS APPROVAL.

The study received approval from the Ethics Committee for Research on Human Subjects of the University of the Witwatersrand prior to commencement (See Appendix D). Those patients who met inclusion criteria were requested, after their discharge from intensive care, to give consent for the use of the laboratory information that had been obtained while they were ill.

9. STUDY DESIGN AND DATA MANAGEMENT.

The study conforms to a cross sectional design.

Data are presented as mean ± 1 standard deviation (SD).

The laboratory results for serum and urine variables and the calculations of MEFWC, CNa and UK/UNa ratio for each sub-group were compared using one-way analysis of variance (ANOVA).

Stata 2014 software was used to determine the statistical significance of the data, a p-value of less than 0.05 was considered significant.

10. RESULTS.

A total of 32 patients meeting the inclusion criteria were entered into the study. At the time of recruitment every patient was in receipt of mechanical ventilated and a combination of intravenous 0.9% saline and an enteral feed.

Following calculation of MEFWC and CNa values each patient was allocated to the appropriate sub-group. UK/UNa ratio was calculated for each patient. Table 1 shows the distribution of patients between the sub-groups. There were no patients in sub-group N1. Consequently there is no information in the table regarding this sub-group. In sub-group N2 there were 9 patients and sub-group N3 there were 10 patients. Sub-groups P1, P2 and P3 consisted of 4, 5 and 4 patients, respectively. Table 1 also shows the patients' age in years (mean ± 1 SD) and distribution of patients according to gender, neurological pathology and operative status per sub-group. Age differences between the sub-groups did not reach statistical significance.

Description	Subgroup					Totals
	N2	N3	P1	P2	P3	
Number of Patients	9	10	4	5	4	32
Age (years) [Mean ± 1SD]	48.3 ± 10.7	34.6 ± 12.8	44.5 ± 9.6	44.6 ± 23.9	42.0 ± 7.8	
Gender:						
Number of males	7	8	4	3	4	26
Number of females	2	2	0	2	0	6
						32
Neurological pathology:						
Intracranial haemorrhage						
- Traumatic origin	3	4	1	1	2	11
- Non-traumatic origin	2	1	2	0	1	6
Intracranial infection	2	3	0	2	0	7
Intracranial neoplasia	2	2	1	2	1	8
						32
Operative state:						
No operation	5	0	1	2	1	9
Post-operation	4	10	3	3	3	23
						32

Table 1: Distribution of patients according to subgroup, age, gender, neurological pathology and operative state. (Note: there is no information relating to sub-group N1 because there were no patients in this sub-group).

Table 2 shows the laboratory results for serum sodium, potassium and osmolality in the study patients. There was no statistically significant difference for any of these variables between the 5 sub-groups of patients.

Table 3 shows the laboratory results for urine sodium, potassium, urine osmolality and volume in the study patients. The urine potassium and urine osmolality results were not statistically different between the sub-groups. There were, however, a number of differences in the results for urine sodium and urine volume. The lowest urine sodium values were found in sub-group P1 (33.50 ± 13.10 mmol/ l) and these were statistically different to the urine sodium values of sub-groups N2, N3 and P3 but not to sub-group P2. The highest urine sodium values were found in sub-group N3 (175.40 ±

30.74 mmol/ l) and were significantly different to values in all the other sub-groups. The second highest urine sodium values were found in sub-group N2 (134.33 ± 20.60 mmol/ l) and these values were also significantly different to those of all the other sub-groups. Urine sodium values for sub-groups P2 (63.00 ± 14.90 mmol/ l) and P3 (93.00 ± 18.11 mmol/ l) were both statistically different to the values found in sub-groups N2 and N3, but not to each other. The value for sub-group P3 was different to that of sub-group P1 as already noted. These results indicate that when hyponatraemic patients are separated into those with a negative and those with a positive result for electrolyte-free water clearance, then some statistical differences in urine sodium losses become apparent. However, there is still enough overlap of values that make it impossible, on the basis of urine sodium alone, to distinguish between patients in sub-groups P1 and P2 and between those in sub-groups P2 and P3.
The highest urine volumes were recorded in sub-group P3 (273.75 ± 117.57 ml/ hr). The urine volume for sub-group P3 was statistically different to that of all other sub-groups. No statistical differences between urine volumes were found between the sub-groups P1 (47.25 ± 16.64 ml/ hr), P2 (119.20 ± 57.21 ml/ hr), N2 (55.89 ± 18.26 ml/ hr) and N3 (137.50 ± 69.25 ml/ hr).

The calculated values for MEFWC, CNa and UK/UNa ratio are detailed in Table 4 and depicted graphically in Figure 1. Sub-groups N3 and N2 have negative MEFWC with sub-group N3 having the more negative value (- 51.48 ± 32.30 ml/ hr versus - 8.87 ± 7.58 ml/ hr). This difference was not statistically significant. Sub-groups P1, P2 and P3 have positive MEFWC values: 18.00 ± 9.89 ml/ hr, 49.65 ± 46.08 ml/ hr and 60.28 ± 58.75 ml/ hr, respectively. The differences between the three P sub-groups are not statistically different. However, MEFWC values for sub-groups P2 and P3 are statistically different to those of sub-groups N2 and N3 while the value for sub-group P1 is different only to that of sub-group N3. Retention of electrolyte-free water in the presence of hyponatraemia is pathognomonic of SIADH[32]. These findings identify sub-groups N2 and N3 as having SIADH. Sub-groups P1, P2 and P3 do not have SIADH because they exhibit positive MEFWC.

Calculations revealed that the highest CNa value was found in sub-group P3 (195.17 ± 98.32 ml/ hr) with the second highest in sub-group N3 (179.88 ± 86.64 ml/ hr). Although the results for sub-groups P3 and N3 are not significantly different, both values are above the normal range for CNa, previously quoted as 25 – 93.3 ml/ hr.[32]. The lowest values for CNa were found in sub-group P1 patients (11.69 ± 3.10 ml/ hr), values which are below the lower limit of normal. In sub-groups P2 and N2 values for

CNa were 51.74 ± 19.55 ml/ hr and 58.28 ± 18.47 ml/ hr, respectively – results that fall within the normal range for this variable. Comparison of the CNa results of sub-groups P1, P2 and N2 does not reach statistical significance. However, the CNa value for each one of these three subgroups is statistically different to the result found in sub-group P3 and in sub-group N3.

Since CNa is a reflection of TBNa, these results suggest that sub-groups P3 and N3 have increased TBNa, sub-groups P2 and N2 have normal TBNa and sub-group P1 has decreased TBNa. Furthermore, since all sub-groups have a CNa value greater than 8.3 ml/ hr, the loss of sodium in all the study patients is the result of a renal process and not an extra-renal process.

The results for CNa suggest that sub-groups P3 and N3 have excess TBNa and that active excretion of that excess is in progress. In addition it is obvious that retention of electrolyte-free water, present in sub-group N3 and due to the effect of inappropriately increased blood levels of ADH, does not interfere with the ability to remove excess sodium. Sub-group P3 is excreting both sodium and water, indicating the presence of an excess of both substances and the ability to mount a normal physiological correction of the disorders present.

A similar situation exists with sub-groups P2 and N2. Both sub-groups have normal TBNa, sodium losses that are within the normal range and varying degrees of TBH_2O excess. Sub-group N2 is retaining electrolyte-free water, for the same reason as sub-group N3, but is able to excrete sodium unhindered. Sub-group P2 is excreting normal amounts of sodium and, at the same time, is able to correct TBH_2O by excreting electrolyte-free water as needed.

Sub-group P1 patients have both a low sodium excretion and a low electrolyte-free water loss. These results suggest that there are deficits of TBNa and TBH_2O present. While the findings may be viewed in that light, it is important to recognize that the findings also suggest that active conservation of sodium and water is in progress.

Table 4 illustrates the results for calculation of the UK/UNa ratios in the sub-groups. Only sub group P1 has a ratio that is greater than unity (1.95 ± 0.91). Sub-groups P2, P3, N2 and N3 all have ratios that are less than unity and are not statistically significantly different to each other. The result for sub-group P1 is statistically significantly different to the results found in the other 4 sub-groups.

A UK/UNa ratio that is greater than unity suggests the presence of hypovolaemia while values of less than unity suggest that hypovolaemia is not present. In this study, only patients in sub-group P1 exhibit hypovolaemia. These same patients exhibit sub-normal sodium loss and the lowest positive

electrolyte–free water loss. These findings suggest an appropriate physiological response to the presence of hypovolaemia, namely retention of sodium and water. In these patients the most likely cause of hypovolaemia is insufficient replacement of normal obligatory daily losses of sodium and water during the hospitalization period. Patients in sub-groups P2 and P3 have positive electrolyte-free water loss coupled with normal or high sodium loss, respectively, but do not have hypovolaemia. These findings also suggest an appropriate physiological response – in this instance sub-group P2 patients have accumulated, during hospitalization, a water excess but not a sodium excess. That water excess is now being eliminated. Sub-group P3 patients have accumulated both sodium and water excesses, during hospitalization, and both substances are being appropriately eliminated. Consequently, the results make it possible to distinguish between Group P patients with hypovolaemia (sub-group P1) and those without hypovolaemia (sub-groups P2 and P3). In addition, it is possible to distinguish between those Group P patients with hyponatraemia due to increased TBH_2O and TBNa (sub-group P3) and those with hyponatraemia due to an increase in TBH_2O alone (sub-group P2). All Group P patients appear to have responded to the presence of hyponatraemia in an appropriate physiological manner.

Sub-group N2 and N3 patients have SIADH. This fact can be recognized as soon as they are shown to have negative MEFWC. Thus, the study provides a mechanism that distinguishes patients who have SIADH from those who do not. In addition, it becomes clear that some patients with SIADH have a normal TBNa (sub-group N2) and some have an elevated TBNa (sub-group N3). The clinician can distinguish which patients are which by calculating CNa.

The study did not identify any patients with natriuresis combined with hypovolaemia. Such findings would suggest a diagnosis of CSWS. The only patients in this study with evidence of hypovolaemia are those in sub-group P1 and they exhibit a sodium excretion rate which is below normal. That combination is not compatible with a diagnosis of CSWS.

Although this study cannot conclusively disprove the existence of CSWS, it does represent another study that has failed to identify patients with that syndrome.

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
Serum Sodium (mmol/ l)	N2	127.89 ± 4.62	No significant differences between sub-groups				
	N3	130.70 ± 1.83					
	P1	132.00 ± 1.83					
	P2	128.80 ± 3.56					
	P3	132.00 ± 1.41					

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
Serum Potassium (mmol/ l)	N2	4.46 ± 0.72	No significant differences between sub-groups				
	N3	4.29 ± 0.44					
	P1	4.55 ± 0.61					
	P2	4.40 ± 0.41					
	P3	4.08 ± 0.13					

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
Serum Osmolality (mOsm/ kg)	N2	271.78 ± 8.57	No significant differences between sub-groups				
	N3	275.50 ± 3.47					
	P1	277.75 ± 2.36					
	P2	275.80 ± 5.54					
	P3	278.25 ± 1.26					

Table 2: Results for serum sodium concentration (upper panel), serum potassium concentration (middle panel) and serum osmolality (lower panel) presented as mean ± 1 SD for each patient sub-groups. No statistically significant differences were found between sub-groups for any of the 3 variables.

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
Urine Sodium (mmol/ l)	N2	134.33 ± 20.60		0.0050	0.0000	0.0001	0.0428
	N3	175.40 ± 30.74	0.0050		0.0000	0.0000	0.0000
	P1	33.50 ± 13.10	0.0000	0.0000			0.0088
	P2	63.00 ± 14.90	0.0001	0.0000			
	P3	93.00 ± 18.11	0.0428	0.0000	0.0088		

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
Urine Potassium (mmol/ l)	N2	40.46 ± 13.13	No significant differences between sub-groups				
	N3	37.90 ± 26.08					
	P1	60.80 ± 22.37					
	P2	30.86 ± 16.30					
	P3	26.68 ± 9.26					

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
Urine Osmolality (mOsm/ kg)	N2	661.22 ± 152.47	No significant differences between sub-groups				
	N3	599.50 ± 135.29					
	P1	816.50 ± 247.40					
	P2	513.40 ± 262.51					
	P3	548.25 ± 222.20					

Variable	Subgroup	Result		Statistical Evaluation: p-values				
		Mean	1 SD	Multiple Comparisons				
				N2	N3	P1	P2	P3
Urine Volume (ml/ hr)	N2	55.89	18.26					0.0000
	N3	137.50	69.25					0.0068
	P1	47.25	16.64					0.0001
	P2	119.20	57.21					0.0068
	P3	273.75	117.57	0.0000	0.0068	0.0001	0.0068	

Table 3: Results for urine sodium (uppermost panel), urine potassium (upper middle panel), urine osmolality (lower middle panel) and urine volume (lowermost panel) presented as mean ± 1 SD for each patient sub-group. Only p-values of less than 0.05 are shown. A blank space or appropriate comment in the p-value columns indicates that a result is not statistically significant.

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
MEFWC	N2	- 8.87 ± 7.58				0.0264	0.0126
	N3	- 51.48 ± 32.30			0.0106	0.0001	0.0000
(ml/ hr)	P1	18.00 ± 9.89		0.0106			
	P2	49.65 ± 46.08	0.0264	0.0001			
	P3	60.28 ± 58.75	0.0126	0.0000			

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
CNa	N2	58.28 ± 18.47		0.0016			0.0073
	N3	179.88 ± 86.64	0.0016		0.0007	0.0058	
(ml/ hr)	P1	11.69 ± 3.10		0.0007			0.0020
	P2	51.74 ± 19.55		0.0058			0.0130
	P3	195.17 ± 98.32	0.0073		0.0020	0.0130	

Variable	Sub-group	Result	Statistical Evaluation: p-values				
		Mean ± 1 SD	Multiple Comparisons				
			N2	N3	P1	P2	P3
UK/UNa	N2	0.31 ± 0.12			0.0000		
Ratio	N3	0.22 ± 0.15			0.0000		
	P1	1.95 ± 0.91	0.0000	0.0000		0.0000	0.0000
	P2	0.49 ± 0.24			0.0000		
	P3	0.29 ± 0.11			0.0000		

Table 4: Calculation results for MEFWC (upper panel), CNa (middle panel) and UK/UNa ratio (lower panel) presented as mean ± 1 SD for each patient sub-group. Only p-values of less than 0.05 are shown. A blank space in the p-value columns indicates that a result is not statistically significant.

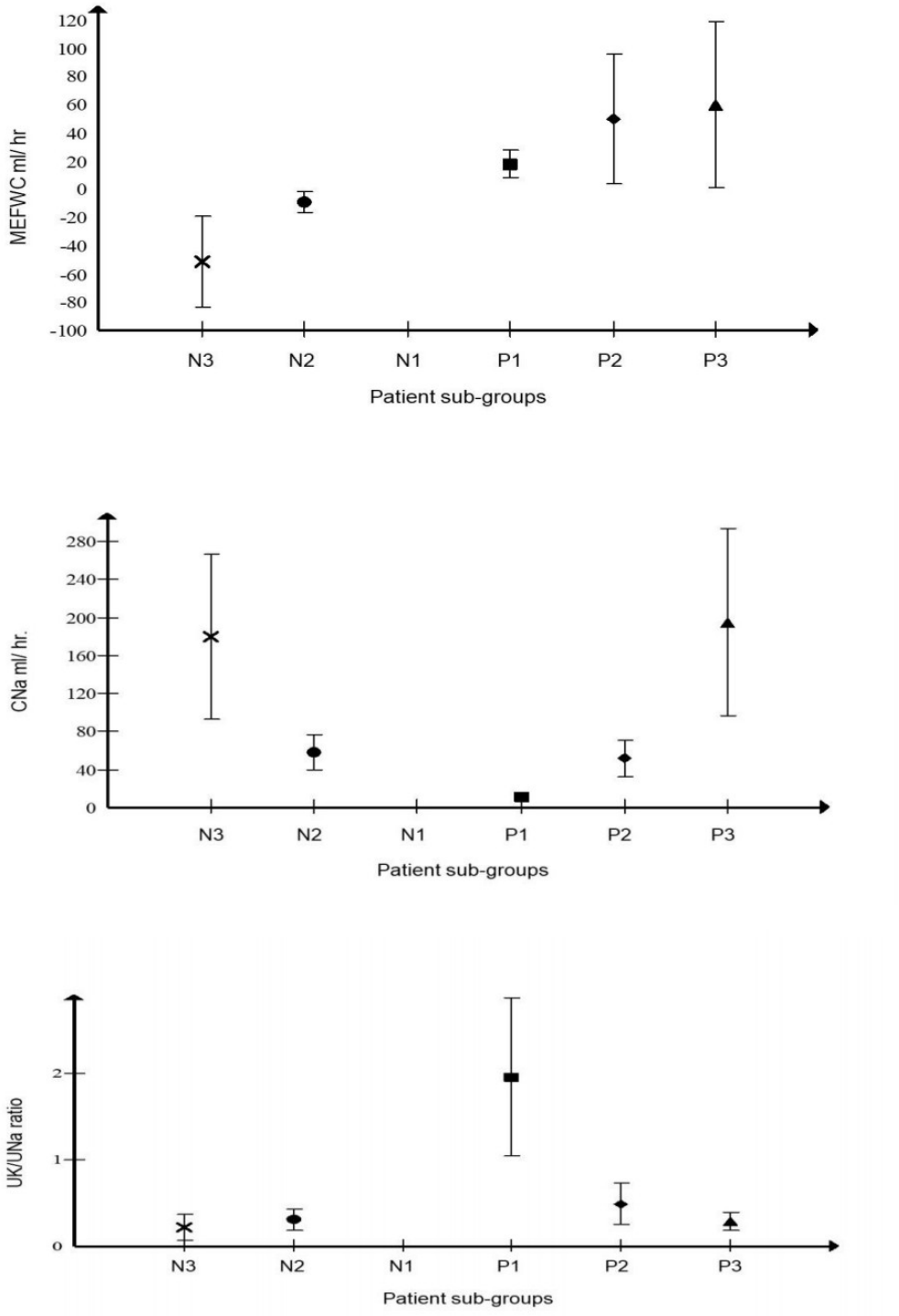


Figure 1: MEFWC (upper panel), CNa (middle panel) and UK/UNa ratio (lower panel) for each patient sub-group (the error bars for sub-group P1 in the middle panel are too close to the mean value marker to be visible).

11. DISCUSSION.

The importance of hyponatraemia a risk factor for mortality in all hospitalized patients, not just those with central nervous system pathology, has been reviewed by Asadollahi *et al*[40]. The importance of determining the cause of hyponatraemia has been stressed and various classifications of causation have been published[2, 41]. Algorithms using a clinical assessment of a patient's extracellular fluid volume as a starting point to determine the cause of hyponatraemia have been proposed[1]. While valuable and helpful, these algorithms require the clinician to determine whether a patient is euvolaemic, hypervolaemic or hypovolaemic before moving to the next step in the algorithm. Making an accurate clinical assessment of extracellular volume has been shown to be difficult[28].

Among the many causes of hyponatraemia are SIADH and CSWS. The two syndromes have different causation, have completely different medical management and cannot be distinguished from each other on the basis of SNa, Sosm, UNa, Uosm or urine output.

Since there is no simple method to differentiate SIADH from CSWS various efforts have been made to obtain other clues. Criteria for SIADH proposed by Janicic and Verbalis[15] were subsequently found to be unable to distinguish between SIADH and CSWS[1]. Other researchers concentrated on finding a variable or variables, serum or otherwise, that would either specifically identify one syndrome or the other or assist in distinguishing one syndrome from the other. Plasma urea and uric acid levels have been evaluated in an elderly population group but did not provide definite answers[27]. Although plasma uric acid was found to be low in a majority of patients with SIADH, this finding is not confined to such patients. Plasma urea levels are not always low in patients with SIADH as might be expected in patients who are retaining water.

Serum ADH levels are not useful – SIADH has been diagnosed in patients in whom serum levels of that hormone could not be detected[42].

Central venous pressure (CVP) has been proposed as a useful measurement, a pressure of less than 5 centimetres of water in a hyponatraemic patient being suggested as diagnostic of CSWS[43]. CVP measurement is fairly easy to arrange for patients in Intensive Care Units, such as those presented in this thesis, but it is probably less so in other areas of a hospital. In addition low CVP does not always indicate the presence of hypovolaemia. The study presented in this thesis was able to avoid CVP measurement by employing UK/UNa ratio as a measure of hypovolaemia. A ratio of more than unity was only found in patients belonging to one sub-group. Those same patients had similar characteristics in the form of a low CNa and low MEFWC. However, it must be admitted that

those two characteristics were not statistically significantly different to a sub-group of patients with normal CNa who had UK/UNa ratio of less than unity.

A study conducted in a group of non-neurosurgical patients with hyponatraemia evaluated the fractional excretion of sodium (FENa) before and after an intravenous infusion of two litres of 0.9% saline given over a 24 hour period[27]. In the study the authors demonstrated that patients with SIADH could be identified by an increase in baseline FENa of more than 0.5%, after saline infusion, but without an increase in baseline plasma sodium. Combinations of change in FENa pre- and post-saline infusion and change in plasma sodium were also able to identify causes of hyponatraemia in groups of patients who did not have SIADH. Although biochemical measurements on two consecutive days and a 24 hour intravenous saline infusion are required to obtain the necessary information, this is important clinical information. In the study presented in this thesis there was no need for a fluid load to be administered to patients and a single 1-hour urine collection providing same-day urine biochemistry information was all that was required to calculate MEFWC, CNa and UK/UNa ratio.

In conclusion, the study presented in this thesis used 3 indices - MEFWC, CNa and UK/UNa ratio - to determine causes of hyponatraemia in a group of 32 patients in a NSICU. The information from the indices was able to identify a group of patients with hyponatraemia, negative values for MEFWC and UK/UNa ratio of less than unity – the latter index suggesting absence of hypovolaemia. The combination of hyponatraemia, water retention and absence of hypovolaemia is diagnostic of SIADH. In addition, these patients could be separated into those with normal TBNa and those with increased TBNa on the basis of their individual CNa result.

It was also possible to identify patients who do not have SIADH on the basis of hyponatraemia co-existing with positive values for MEFWC. These patients exhibited low, normal or high values for CNa, indicating their variable TBNa status. The sub-group of patients with positive MEFWC and low CNa exhibited UK/UNa ratios of more than unity. These findings suggest retention of sodium as a consequence of low TBNa and hypovolaemia. The study did not identify any patient with a combination of hypovolaemia and either normal or increased CNa. Such combinations would suggest a diagnosis of CSWS.

This study has not proved that CSWS does not exist; it only indicates that no patient could be identified as suffering from CSWS. However, it does represent another study that has failed to identify patients with that syndrome.

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13. APPENDICES

Appendix A: Participant information sheet

Title of Study: The use of free water clearance to distinguish between Syndrome of Inappropriate Anti Diuretic Hormone Secretion (SIADH) and Cerebral Salt Wasting Syndrome (CSWS) in hyponatremic patients in neurosurgical ICU

Introduction:

Dear Mr/Mrs/Miss/Ms……
Good Morning to you.
My name is Victor Magumbeze and I am a doctor in the Department of Neurosurgery. I wish to conduct some research into a problem that is common in patients like yourself who have suffered an illness or injury to the brain. Research is the process to learn the answer to a question.
There are two illnesses which reduce the amount of sodium in the blood of people like yourself arising as a result of the illness that has affected you. The problem is fairly easy to treat and you will be receiving the correct treatment at all times. The difficulty for us is distinguishing between the two main causes of low blood sodium as fast as possible. We think that if we measure the amount of sodium and the amount of water passed in urine we will be able to determine more quickly which of the two forms of the illness is affecting you. One of our objectives is to decrease the time taken to determine which cause is affecting a person. However, this does not mean that you will be subjected to any delay in treatment. The treatment of these problems is well established and is started immediately and refined as results are obtained from the laboratory. Our objective is to decrease the time taken to obtaining the exact causation (or diagnosis in our language).
The way we would investigate the problem is as follows:

a. We will collect two urine samples, one hour after the problem is recognised and 24 hours after the problem is recognised
b. These urine samples will be sent to the laboratory for measurement of sodium, potassium and osmolality

The urine passed by your kidneys is being automatically collected in a bag at the side of your bed. The samples that we want will be taken from that bag. Therefore the collection of urine samples will not require any effort on your part nor will it lead to any discomfort for you.
In this study I would like to determine if a formula for calculating free water clearance can distinguish between the two diagnoses.

Invitation to participate:
I would like to invite you to participate in the following study which is considering the use of a mathematical formula to differentiate between the two conditions which causes a low sodium in a quick and efficient way as the treatment for these two conditions are different.
These two conditions are called Syndrome of Inappropriate Anti Diuretic Hormone Secretion (SIADH) in which the body abnormally retains water and Cerebral Salt Wasting (CSW) in which the body abnormally loses salt these two conditions may have a similar clinical picture but their treatment is different.

What is involved in participating in the study?

Study Design:

- Routine blood tests will be done on you as required to treat your condition, but a mathematical formula is used to categorise your condition as SIADH or CSW
- You will be in the study as long as your body sodium which is part of the salt is <135 until corrected
- In this study there is no questionnaire involved as only your clinical data is used

Risks/Benefits for participating in the study:

- There is no risk or additional benefits associated with the study as the data used and treatment offered does not differ whether you are involved in the study or not

Participation:

- Participation in the study is voluntary
- You can chose to withdraw from the study without any reason or explanation with no risk, penalty, loss of benefit or care to which you are otherwise entitled to.
- There is no financial gain involved in participating in this study, nor is there any cost to you.
- If you agree to participate, you will be asked to sign an Informed Consent Sheet

Confidentiality/ Anonymity:

- Confidentiality will be maintained at all possible times by use of a coding system where serial numbers are allocated to data sheets instead of actual names but however absolute confidentiality may not be maintained for example if the data is required by law enforcement or quality control.

Contact Details:

- If you have any queries do not hesitate to contact myself Dr V Magumbeze at 063 026 5198, or Dr C Clinton my supervisor at 011 488 3565
- This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

- If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for taking the time to read this information sheet.

May 2018

Appendix B: Information sheet for patient's next-of-kin.

Information sheet for deferred consent or relatives consent
Title of Study: The use of free water clearance to distinguish between Syndrome of Inappropriate Anti Diuretic Hormone Secretion (SIADH) and Cerebral Salt Wasting Syndrome (CSWS) in hyponatremic patients in neurosurgical ICU

Introduction:

Dear Mr/Mrs/Miss/Ms……
Good Day to you.
My name is Victor Magumbeze and I am a doctor in the Department of Neurosurgery. I wish to conduct some research into a problem that is common in patients like your relative who have suffered an illness or injury to the brain. Research is the process to learn the answer to a question. I would like to enrol your relative Mr/Mrs/Miss/Ms …… In the study outlined below.

Please find below an information sheet that would have been given to your relative to sign if he/she was able to do so. And we will get consent from your relative at any time when he/she is able to do so and they are free to refuse to be part of the study should they not feel like it, without giving any reason and without having his/her treatment being compromised in any way.
There are two illnesses which reduce the amount of sodium in the blood of people like your relative arising as a result of the illness that has affected him/her. The problem is fairly easy to treat and he/she will be receiving the correct treatment at all times. The difficulty for us is distinguishing between the two main causes of low blood sodium as fast as possible. We think that if we measure the amount of sodium and the amount of water passed in urine we will be able to determine more quickly which of the two forms of the illness is affecting him/her. One of our objectives is to decrease the time taken to determine which cause is affecting a person. However, this does not mean that he/she will be subjected to any delay in treatment. The treatment of these problems is well established and is started immediately and refined as results are obtained from the laboratory. Our objective is to decrease the time taken to obtaining the exact causation (or diagnosis in our language).
The way we would investigate the problem is as follows:

c. We will collect two urine samples, one hour after the problem is recognised and 24 hours after the problem is recognised
d. These urine samples will be sent to the laboratory for measurement of sodium, potassium and osmolality

The urine passed by his/her kidneys is being automatically collected in a bag at the side of his/her bed. The samples that we want will be taken from that bag. Therefore the collection of urine samples will not require any effort on his/her part, nor will it lead to any discomfort for himher.

In this study I would like to determine if a formula for calculating free water clearance can distinguish between the two diagnoses.

Invitation to participate:

I would like to invite you to participate in the following study which is considering the use of a mathematical formula to differentiate between the two conditions which causes a low sodium in a quick and efficient way as the treatment for these two conditions are different.
These two conditions are called Syndrome of Inappropriate Anti Diuretic Hormone Secretion (SIADH) in which the body abnormally retains water and Cerebral Salt Wasting (CSW) in which the body abnormally loses salt these two conditions may have a similar clinical picture but their treatment is different.

What is involved in participating in the study?

Study Design:

- Routine blood tests will be done on you as required to treat your condition, but a mathematical formula is used to categorise your condition as SIADH or CSW
- You will be in the study as long as your body sodium which is part of the salt is <135 until corrected
- In this study there is no questionnaire involved as only your clinical data is used

Risks/Benefits for participating in the study:

- There is no risk or additional benefits associated with the study as the data used and treatment offered does not differ whether you are involved in the study or not

Participation:

- Participation in the study is voluntary
- You can chose to withdraw from the study without any reason or explanation with no risk, penalty, loss of benefit or care to which you are otherwise entitled to.
- There is no financial gain involved in participating in this study nor is there any cost to you.
- If you agree to let your relative participate, you will be asked to sign an Informed Consent Sheet

Confidentiality/Anonymity:

- Confidentiality will be maintained at all possible times by use of a coding system where serial numbers are allocated to data sheets instead of actual names but however absolute confidentiality may not be maintained for example if the data is required by law enforcement or quality control.

Contact Details:

- If you have any queries do not hesitate to contact myself Dr V Magumbeze at 063 026 5198, or Dr C Clinton my supervisor at 011 488 3565
- This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

- If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for taking the time to read this information sheet.

May 2018

Appendix C: Consent Form

Title of Study: The use of free water clearance to distinguish between Syndrome of Inappropriate Anti Diuretic Hormone Secretion (SIADH) and Cerebral Salt Wasting Syndrome (CSWS) in hyponatremic patients in neurosurgical ICU.

Name of participant or Name of participant's next-of-kin:

_____

I have received, from Dr V. Magumbeze, a participant's information sheet/ information sheet for a patient's next-of-kin relating to the above study and have had an opportunity to read the same and to ask questions about the study.

I hereby give consent for my / my relative's medical records/ laboratory results to be used for the purposes of medical research in the above-named study.

Signature: _____ Date: _____

(Patient participant or Patient's next-of-kin)

I **do not** give consent for my / my relative's medical records/ laboratory results to be used for the purposes of medical research in the above-named study.

Signature: _____ Date: _____

(Patient participant or Patient's next-of-kin)

Appendix D: Work Sheet

WORK SHEET PAGE 1

Research Project:

The use of free-water clearance to distinguish between the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and Cerebral Salt-Wasting Syndrome in hyponatraemic patients in Neurosurgical Intensive Care Unit.

Researcher: Dr V. Magumbeze

Supervisors: Dr C. Clinton, Dr J. Ouma

Patient details:

Name:_____

Age: :_____

Gender: :_____

Hospital File No:_____

Date of Admission: :_____

Patient allocation tracking number:_____

WORK SHEET PAGE 2

Researcher: Dr V. Magumbeze Supervisors: Dr C. Clinton, Dr J. Ouma.

Patient allocation tracking number:_____

Laboratory variables:

Serum Sodium:_____

Serum Potassium:_____

Serum Osmolality:_____

Urine Sodium:_____

Urine Potassium:_____

Urine Osmolality:_____

Urine Volume:_____

Calculations:

MEFWC:_____

CNa:_____

UK/UNa:_____

Group / Sub-group allocation:

N1 N2 N3 P1 P2 P3

Appendix E: Ethics Committee Clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr V Magumbeze

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M171029

NAME: (Principal Investigator)	Dr V Magumbeze
DEPARTMENT:	School of Clinical Medicine Department of Surgery Division of Neurosurgery Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The use of free water clearance to distinguish between the Syndrome of Inappropriate Anti-Diuretic Hormone Secretion (SIADH) and Cerebral Salt Wasting Syndrome (CSWS) in hyponatraemic patients in Neurosurgical ICU
DATE CONSIDERED:	27/10/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs C Clinton and J Ouma
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/05/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr V Magumbeze
School of Clinical Medicine
Department of Surgery
Division of Neurosurgery
Charlotte Maxeke Johannesburg Academic Hospital

E-mail: vmagumbeze@yahoo.co.uk

CC: Supervisor: Drs C Clinton and J Ouma <cclinton@doctors.org.uk>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 02/05/2018

REF: *R14/49*

PROTOCOL NO: **M171029** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *The use of free water clearance to distinguish between the Syndrome of Inappropriate Anti-Diuretic Hormone Secretion (SIADH) and Cerebral Salt Wasting Syndrome (CSWS) in hyponatraemic patients in Neurosurgical ICU*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.



MSWorks2000/Iain0007/Clearscan.wps