

ORIGINAL ARTICLE

Comparison between Urine Sodium and Clinical Evaluation to Assess Saline Responsiveness in Severe Hyponatremia - A Prospective Study

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Abstract

Introduction and Background: Hyponatremia is a commonly encountered electrolyte disturbance seen in diverse clinical settings. The recently published European guidelines comprehensively summarize the present status of evaluation for hyponatremia. The guidelines emphasize the poor predictability of clinical criteria and instead suggest that the urine sodium (U_{Na}) may be a better way to initially evaluate the cause of hyponatremia.

Aims and Objectives: Aim of the study is to comparison between urine sodium and clinical evaluation to assess saline responsiveness in severe hyponatremia.

Materials and Methods: Prospective Cross sectional study carried out in Departments of Nephrology, Kerala Institute of Medical Sciences, Thiruvananthapuram, Kerala. Study Period between October 2014 to October 2016 (2 years), Patients diagnosed as Severe hyponatremia S.Sodium < 125mEq/L based on clinical and laboratory evaluations

Inclusion Criteria: All clinically and lab confirmed cases of severe hyponatremia, Age >18 years. Outpatients, Inpatients admitted to medical wards and ICU, who give informed consent and serum sodium of less than 125mEq/L constitute the study population. These patients meeting the following criteria: blood glucose level less than 200mg/dl would be included.

Exclusion Criteria: Patients with overt hypervolemia due to cardiac, hepatic, and renal disease with gross edema were excluded.

Results: Among 50 patients in the study 70% were found at age group > 60 yrs. 30% patients were < 60 years age group. Youngest patient was 14 yrs old and oldest patient was 83 yrs old. 21 (42%) were Females and Males were 29 (58%). Majority of the cases were symptomatic at time of presentation n=38 (76%). All were having hypotonic hyponatremia among them 14 patients (28%) were euvoletic, 3 patients (6%) were hypervolemic and 33 patients (66%) were hypovolemic. 31 patients (62%) had serum Sodium levels between 115-125mEq/L and 19 patients (38%) had serum Sodium levels between 100-114mEq/L. Among the 33 patients (66%) Hyponatremia due to volume depletion by clinical assessment by the Nephrologist and who were given saline 26 (78%) were saline responsive and 7 patients (22%) were saline non responsive. Among the 7 patients who are saline non responders 6 patients (85.7%) had $U_{Na} > 20$ and 1 patient (14.3%) had $U_{Na} < 20$, which is statistically not significant ($p=0.840$). Among the 44 patients who are saline responders 18 patients are saline responsive. Among the 44 patients 20 (76.9%) had $U_{Na} > 20$ and 6 (23.1%) had $U_{Na} < 20$, statistically not significant ($p=0.604$). Duration for normalizing sodium was noted during the study 17 cases, 1-3 days were needed, 22 cases needed 4-7 days.

Conclusion: Volume status of patients with hyponatremia can be assessed clinically with a high degree of reliability if the hyponatremia is severe. Thus we re-emphasize the importance of measuring volume status in patients with hyponatremia and classify patients on basis of volume status prior to triaging management. The measurement of U_{Na} had a poor correlation with saline responsiveness and this shows that the laboratory measure is subject to errors due to prior treatments given to the patient and has to be interpreted with the prior clinical scenario in mind.

Introduction and Background

Hyponatremia is a commonly encountered electrolyte disturbance seen in diverse clinical settings.^{1,2} In 1962, Leaf first proposed that clinical assessment of extracellular fluid volume status provides a useful means of evaluating the cause and of selecting the appropriate therapy in hyponatremic patients.³ Barring a few instances, in all cases of hyponatremia vasopressin levels are elevated either

appropriately or inappropriately and this leads to the low sodium levels seen. Treatment depends on identifying the cause of raised vasopressin levels which can then lead to a proper fluid and salt management. Identifying the cause of raised vasopressin levels will need proper evaluation of Extracellular Fluid (ECF) volume status and effective arterial blood volume. Previous trials have shown very poor correlation between clinical evaluation of ECF volume and response to isotonic saline.

Therefore, we need readily available and reliable parameters to reliably evaluate ECF volume.^{4,5}

The recently published European guidelines comprehensively summarize the present status of evaluation

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for hyponatremia. The guidelines emphasize the poor predictability of clinical criteria and instead suggest that the urine sodium (U_{Na}) may be a better way to initially evaluate the cause of hyponatremia.^{1,6-8}

The guidelines further state that ECF volume status can be assessed only after triaging by means of assessment of U_{Na} . However, the recommendations in the guidelines are based on two clinical studies which have evaluated the clinical assessment of volume status in patients with relatively mild hyponatremia.^{1,9,10} It is our hypothesis that in patients with severe hyponatremia, ECF volume status can be reliably predicted by clinical criteria and that is the basis of this study.

Aims and Objectives

Aims

Aim of the study is to comparison between urine sodium and clinical evaluation to assess saline responsiveness in severe hyponatremia.

Objective

To find out the effectiveness of urine sodium or clinical evaluation in deferring response to saline in hyponatremia.

Research question

1. What is the use of clinical parameters predicting the cause of hyponatremia and saline responsiveness?
2. What is the reliability of urine spot sodium in determining the saline responsiveness in severe hyponatremia?

Materials and Methods

Study Site

This prospective study was carried out in Departments of Nephrology, Kerala Institute of Medical Sciences, Thiruvananthapuram, Kerala.

Study Population

Patients diagnosed as Severe hyponatremia $S_{Na} < 125\text{mEq/L}$ based on clinical and laboratory evaluations.

Study Design

Prospective Cross sectional study

Study Period

October 2014 to September 2016 (2 years)

Sample Size

The following formula is used to calculate sample size:

$$n = (Z1-\alpha/1 + Z1-\beta)^2 \times n^2 / \delta^2$$

Where, n = Sample size

$Z\alpha/1 = 1.96$ at 5% level of significance

$Z\beta = 0.842$ at 80% power

δ = desired precision, applying this formula, the sample size $n = 50$ cases.

Inclusion Criteria

All clinically and lab confirmed cases of severe hyponatremia, Age > 18 years. Outpatients, Inpatients admitted to medical wards and ICU, who give informed consent and serum sodium of less than 125mEq/L constitute the study population. These patients meeting the following criteria: blood glucose level less than 200mg/dl would be included.

Exclusion Criteria

Patients with overt hypervolemia due to cardiac, hepatic, and renal disease with gross edema were excluded.

Consent and Ethics

Approval of the institute's scientific and ethical committee was taken for conducting the study.

Methodology

Method of measurement of outcome of interest

Study population included patients with hyponatremia who have been seen by a Nephrologist and volume status assessment has been done by the Nephrologist. In laboratory confirmed hyponatremia patients admitted in wards and ICU of KIMS hospital from January 2015 to January 2017. Informed consent was taken. Detailed history and physical examination was carried out at the time of admission.

5 ml Blood was withdrawn by Laboratory staff for blood tests and 5ml urine sample for urinary sodium estimation by Ion selective electrode equipment at NABL accredited lab of KIMS hospital.

Just before starting the saline infusion, a clinical examination of volume status (by a Nephrologist) and biochemical evaluation was carried out, including a "spot" urine sample. Extracellular fluid volume was evaluated clinically by a Nephrologist by the means of mucosa hydration, skin

turgor, jugular venous pressure, and orthostatic changes in pulse and blood pressure. Serum sodium, chloride, potassium (measured by ion-selective electrode) blood urea, serum creatinine, serum uric acid, and serum osmolality were measured.

All patients deemed to be hypovolemic by the currently recommended urine sodium criteria and then by clinical assessment received an infusion of 2 L 0.9% sodium chloride over 24 hours with intermittent monitoring of serum sodium status. Thereafter, fluid management was based on clinical status and further evaluation of serum sodium status. Patients were labeled as saline-responders group (SR) if they have a sustained increase in plasma sodium of at least 5mmol/L following saline infusion. The remaining patients were considered to be saline-non responders group (SNR).

Data collection methods

Clinical evaluation of patients' hydration status done by a Nephrologist at the time of diagnosis. Serum electrolytes and urine spot sodium done at the time of diagnosis.

Statistical analysis

The data was entered into M.S. Excel and was analysed using the statistical software SPSS version.16.0. The entire continuous variables were expressed in mean and standard deviation. The two groups were compared using paired "t" test. p value < 0.05 was considered statistically significant.

Observations and Results

This study entitled "**Comparison between urine sodium and clinical evaluation to assess saline responsiveness in severe hyponatremia- a prospective study**". Recruited $n = 50$ patients. Observations are as follows.

At presentation $n = 50$ patients Out of them 46 patients (92%) had a pulse rate below 100/min and 4 patients (8%) had pulse rate above 100/min. 20 patients (40%) had SBP below 110/mm of hg and 30 patients (60%) had SBP above 110/mm of hg. 35 patients (70%) had DBP below 70/mm of hg and 15 patients (15%) had DBP above 70/mm of hg.

Among the patients, who were diagnosed hyponatremia due to volume depletion by clinical assessment by

Table 1: Various attributes in the present study

Attributes	Number (n=50)	Percentage
Age <60 yrs	15	30
>60 yrs	35	70
Female	21	42
Male	29	58
Nausea	8	16
Vomiting	8	16
Fatigue	8	16
Hiccups	6	12
Lethargy	3	06
Muscle cramps	2	04
Seizure	3	06
T2DM	8	16
HTN	5	10
CAD	5	10
COPD	1	2
CA lung	1	2
Euvolemic	14	28
Hypervolemic	3	6
Hypovolemic	33	66
Serum Sodium 115-125	31	62
Serum Sodium 100-114	19	38

the Nephrologist and who were given saline 26 (78%), were saline responsive.

Among the patients who were diagnosed hyponatremia due to volume depletion and who were given saline 7 (22%) were saline non responsive.

Among the 50 patients, 4 (8%) received 3% NaCl 100ml for their symptomatic hypovolemia, 1(2%) patient was not given 3% NaCl even after advise, 1(2%) had taken frusemide before coming to our hospital, 1(2%) patient diuretic was given in emergency room suspecting hypervolemia, 1(2%) saline was given before taking urine spot sodium, 1(2%) patient was given saline outside before in a local hospital and 1(2%) was treated purely by increasing salt intake without 3%NaCl.

Among the 50 patients whose volume status was assessed by Nephrologist and Urine spot sodium measured, the mean S.Na before treatment was 114±5.5 mEq/L, the mean S.Na after treatment was 119±6.2 mEq/L. which is statistically significant ($p < 0.001$).

This table shows the association between SNR and UNa. Out of the 24 patients 7 patients are saline Non responsive. In that 6 (85.7%) had UNa > 20 and 1 (14.3%) had UNa < 20, which was statistically not significant (0.840).

This table shows the association between SR and UNa. Out of the 44 patients, 18 patients were saline

responsive. In that 20 (76.9%) had UNa > 20 and 6 (23.1%) had UNa < 20, which was statistically not significant (0.604).

Days for normalising sodium were noted during the study 17 cases needed 1-3 days were needed, 22 cases needed 4-7 days.

Discussion

The recent guidelines published by the European group have commented on the poor reliability of clinical evaluation of volume status in categorizing hyponatremia. The comments were based on two studies which were done in patients with mild to profound hyponatremia. However, our hypothesis was that in patients with profound hyponatremia, it is much easier to categorize patients by volume status and in any case, it is this group that requires more careful management of hyponatremia. The guidelines quoted above have also put Urine Na concentration to be more reliable than that of clinical criteria. This study was undertaken to re-emphasize the importance of clinical examination of volume status in estimating the cause of hyponatremia.

The study recruited n=50 patients with the following observations:

Table 1 shows 70% were found at age group > 60yrs. 30% patients were < 60 years age group. Youngest patient was 14 yrs old and oldest patient was 83yrs old. In this study, out of the total n=50 patients, 21 (42%) were females and males were 29 (58%).

Table 1 shows majority of the cases were severely symptomatic at time of presentation n=38 (76%). Out the symptomatic cases, 8 patients (16%) had lethargy, vomiting and fatigue. 6 patients (12%) had Hiccups, 3 patients (6%) had Lethargy and seizures and 2 patients (5%) had muscle cramps. None of the patients had in confusion, dizziness, gait disturbance, coma, obtundation or respiratory arrest.

In a study by Rao et al,¹¹ lethargy, drowsiness with slow response and irrelevant talk were the common presenting symptoms, (4%) patients had seizures. In a study by Mahavir et al.¹² confusion was present in 30% and altered sensorium in 17.1%. 2% had seizures. 14% were asymptomatic. In a study by Devika. et al. majority of the cases were asymptomatic at time of presentation (58%). Out the

symptomatic cases, (42%) had lethargy, (76%) had abnormal behavior, (14%) had postural dizziness and (9%) had seizures. Both the patients had GTCS, had recovered when serum sodium normalized. None of the patients were in coma.

Table 1 shows in the present study n=19 (38%) patients had co-morbidities. Out them 8 patients (16%) had Type II diabetes mellitus, 5 patients (10%) had Systemic hypertension and Coronary artery disease. 1 patient (2%) had Chronic obstructive pulmonary disease and 1 patient (2%) had CA Lung. In study by Vurghese et al.¹³ the common co-morbidities were CCF (18%), CKD (19.69%), HTN (6.06%), DM (6.06%) and cirrhosis (6.06%). In a study by Devika.et.al out of 50 subjects, (30%) were hypertensive, (32%) were diabetic, (36%) had CHF, (4%) had CLD and (4%) were hypothyroid, only 1 patient had CKD. In a study by Rao et al.¹¹ most common co-morbid conditions were HTN (62%), DM (51%), CKD (22%) and IHD (18%).

Table 1 shows Out of 50 patients in the present study all had hypotonic hyponatremia. Out of that 14 patients (28%) were euvolemic, 3 patients (6%) were hypervolemic and 33 patients (66%) were hypovolemic. In a study by Devika et.al Out of the 50 patients, 14 patients (28%) were euvolemic, 19 patients (38%) were hypervolemic, and 17 patients (34%) were hypovolemic. In the study by Miyashita et al. (95%) had hypotonic hyponatremia out of which (63%) had hypovolemia, (5%) had hypervolemia and (32%) euvolemia. In the study by Rao et al,¹¹ (61%) were euvolemic, (23%) were overloaded and (16%) dehydrated. The commonest type of hyponatremia noted in the study was Isovolemic Hypo-osmolar hyponatremia. Our study closely correlates with Miyashita et al.¹⁴

Table 1 shows Out of 50 patients with severe hyponatremia 31 patients (62%) had Serum Sodium levels between 115-125mEq/L and 19 patients (38%) had Serum Sodium levels between 100-114mEq/L Table 2.

Among the patients who were diagnosed hyponatremia in the present study due to volume depletion and who were given saline 7 (22%) were saline non responsive Table 3.

Among the patients who were diagnosed hyponatremia due to volume

Table 2: Comparison between various parameters

	Mean	N	Std. deviation	Std. error mean	t	p-value
S Na before	114.82	50	5.565	0.787	-11.198	<0.001
S Na after	119.76	50	6.209	0.878		

*Statistically significant

depletion in the present study and who were given saline 26 (78%) were saline responsive Table 4.

Among the 50 patients in the present study (6%) were hypervolemic and they were advised fluid restriction and 33 patients (66%) were given saline, 4 patients (8%) received 3% NaCl 100ml for their symptomatic hypovolemia, 1 patient (2%) was not given 3% NaCl even after advise, 1 patient (2%) had taken frusemide before coming to our hospital, 1 patient (2%) diuretic was given in emergency room suspecting hypervolemia, 1 patient (2%) saline was given before taking urine spot sodium, 1 patient (2%) patient was given saline outside before in a local hospital and 1 patient (2%) was treated purely by increasing salt intake without 3%NaCl.

In a study by Devika et al. (54%) had received 3% saline, (44%) were advised fluid restriction, (40%) were given diuretics, (10%) were given normal saline and potassium replacement was given for (8%) of the cases. In the study done by Mahavir et al,¹² 3% saline was given for (48.5%), normal saline for (48.6%), fluid restriction was given for (40%). Our study had a significant number of hypovolemic patients when compared to the above studies.

There was a much poorer correlation between UNa and saline responsiveness Table 3. Only 23% of saline responsive subjects had a UNa less than 20. This is probably because most of them had already received treatment with saline

and Lasix and 3% saline and this had altered their UNa status. This illustrates the difficulty in applying UNa to patients who have already been treated for hyponatremia earlier. Unless UNa is tested prior to starting treatment, this parameter is of no value in planning treatment.

The days for normalising sodium were noted during the study 17 cases, 1-3 days were needed, 22 cases needed 4-7 days. This was similar to a study by Devika et.al. In study by Mahavir et al,¹² time taken for recovery was 3.7 ± 2.4 days.

No complications occurred due to treatment of hyponatremia in the present study. Thus the study emphasizes the utility of clinical evaluation of volume status in assessing patients prior to treatment for hyponatremia. Clinical evaluation of volume status is far more important in the management of patients with profound hyponatremia than UNa which is subject to errors if the patient has been given any prior treatment.

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Table 3: Comparison between urine spot sodium and saline non responders

SNR	UNa		Total	X2	p-value
	< 20	> 20			
No	3	14	17	0.040	0.840
	17.6	82.4	70.8		
Yes	1	6	7		
	14.3	85.7	29.2		
Total	4	20	24		

*Statistically significant

Table 4: Comparison between urine spot sodium and saline responders

SR	UNa		Total	X2	p-value
	< 20	> 20			
No	3	15	18	0.269	0.604
Response	16.7%	83.3%	100.0%		
Response	6	20	26		
	23.1%	76.9%	100.0%		
Total	9	35	44		

*Statistically significant

than do usual clinical and biochemical parameters. *The American Journal of Medicine* 1995; 99:348-355.

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