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Original Article

A Comparative Analysis of Serum Sodium Level Utilizing Direct and Indirect Ion Selective Electrode in Critically Ill Patients with Hypoalbuminemia: Methodological Insights and Clinical Implications

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Abstract

Background: Serum electrolytes are one of the most frequently requested tests in patients from critical care settings. Methods for estimation of serum electrolytes include direct and indirect ion selective electrode (ISE). In case of indirect ISE, the pre-analytical dilution step can result in pseudonormonatremia or pseudohypernatremia in setting of hypoalbuminemia. Discrepancy in sodium results can lead to the misdiagnosis and mismanagement of critically ill patients.
Objective: To evaluate the difference of mean serum sodium level measured by direct and indirect ISE in critically ill patients with hypoalbuminemia.
Study type, settings & duration: This cross-sectional study conducted in Department of Chemical Pathology, Sheikh Zayed Hospital, Rahim Yar Khan from February to August 2022.
Methodology: A total 408 study subjects aged between 20 to 60 years admitted in intensive care units of Sheikh Zayed hospital Rahim yar khan with serum albumin level <3.5 g/dl were included in study. Serum sodium level was estimated concurrently by both methods for all study subjects satisfying the inclusion criteria. Mean difference of serum sodium level measured by both methods was evaluated to see the statistically significant difference between two methods.
Results: Mean difference of serum sodium level measured by indirect and direct ISE (Indirect ISE-direct ISE) was 4.216±13.571mmol/L with statistically significant difference (*p* value: 0.000). The difference was not acceptable according to CLIA (Clinical Laboratory Improvement Amendments) requirements for acceptable performance between the methods. Effect of triglyceride was statistically significant for mean difference of serum sodium level between two methods (*p* value: 0.026). No statistically significant difference of mean difference of serum sodium level with respect to other variables was found.
Conclusion: Interchangeable use of direct and indirect ISE should be avoided in the setting of hypoalbuminemia. Indirect ion selective electrode results of serum sodium level are misleading in the setting of hypoalbuminemia and critically ill patients can be misdiagnosed and mismanaged if sodium level is measured by indirect ion selective electrode. Standardization should be considered by hospital laboratories to use direct ISE for serum sodium measurement.
Key words: Serum sodium level, direct and indirect ion selective electrode, hypoalbuminemia.

Introduction

Serum electrolytes are one of the most frequently requested tests in patients from emergency department or critical care settings and urgent reports are crucial for clinical decision-making.[1] Two methods are recommended for estimation of serum electrolytes, using the principle of an ion-selective electrodes (ISE).[2] Direct and Indirect Ion selective electrode. Indirect ion selective electrode method is used in automated analyzers used in central laboratories and direct ion selective Electrode is used in blood gas analyzers. There is plasma or serum dilution step before analysis in case of indirect ISE.[2] In direct ion selective electrode, the activity of serum electrolytes is measured in plasma without dilution. There is direct contact of plasma or serum sample with the surface of electrode in direct ISE and measurement of relevant ion in the plasma water occur.[3]

Potentiometry is an electrochemical technique that measures the difference of electrical potential in a potentiometric cell between the two electrodes under the condition of essentially zero current. Total volume of the plasma that is occupied by the solids is excluded by the electrolytes in case of electrolyte exclusion effect. 93% plasma volume is water and 7% of plasma is occupied by the solids primarily proteins and lipids. The main electrolytes including sodium, potassium, chloride and bicarbonate are confined to the plasma water phase. The exclusion effect of electrolytes become troublesome in certain situations which alter the volume of plasma water such as hyperproteinemia, hyperlipidemia and hypoabuminemia.[4]

Pseudohypernatremia can be defined as spuriously increased concentration of serum sodium >145 mmol/L due to hypoproteinemia. Normal physiological conditions maintain the electro-neutrality in our body and concentration of serum sodium is maintained within the reference limit of 135-145 mmol/L and serum sodium level less than 135 mml/L is diagnosed as hyponatremia and concentration more than 145 mmol/L is diagnosed as hypernatremia.[5]

Serum albumin is the most abundant protein in human plasma. Around half of the serum protein is constituted by Albumin.[6] Range for the concentration of albumin in serum is 3.5-5.0 g/dl. Causes of hypoalbuminemia include chronic or acute medical conditions such as hepatic cirrhosis, nephrotic syndrome, malnutrition, heart failure and acute or chronic inflammatory conditions. Lower levels of serum albumin are associated with greater risk of mortality and morbidity among hospitalized patients.[6] The distribution of electrolytes in intracellular and extracellular environment is very important for fluid distribution and to maintain the elctroneutrality.[7,8]

Sodium disorders such as hypernatremia and hyponatremia are common disorders of electrolytes.[9,10] Accurate estimation of serum sodium is very important, as misdiagnosis and mismanagement can lead to many complications that may be life threatening for the patient.[11,12] Discrepancy in sodium results can occur in patients admitted in intensive care units due to many conditions.[13] Plasma water displacement due to abnormal concentration of solids such as lipids and proteins affect the pre-analytical dilution step in case of indirect ISE and it results in pseudohyponatremia, pseudonormonatremia or pseudohypernatremia.[14] Likewise, the method for estimation of serum sodium in case of abnormal solids concentration such as hyperlipidemia and hypoalbuminemia should be preferably direct ISE.[15]

The objective of our study is to evaluate the difference of mean serum sodium level measured by direct and indirect ion selective electrode in critically ill patients with hypoalbuminemia. Our aim is to provide clear guidance to lab personnel regarding difference of mean serum sodium levels measured by direct and indirect ion selective electrode. Difference of mean serum sodium level measured by both methods (Direct and indirect ion selective electrode) will provide direction to lab personnel as well as clinicians that how much sodium results can vary in case of hypoalbuminemia. Misclassification of electrolyte status can lead to misdiagnosis and mismanagement of critically ill patients. On the basis of this study, misdiagnosis and mismanagement of patients can be prevented by keeping in view the true difference in mean serum sodium levels measured by both methods.

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Authors Contribution

RT & SSH conceptualized the project. RT did the data collection. RT & MS performed the statistical analysis. SSH & MS did the literature search. Drafting, revision & writing of manuscript were done by RT, SSH & MS.

Methodology

Cross-sectional study conducted in Chemical Pathology section, Department of Pathology, Sheikh Zayed Hospital, Rahim Yar Khan from February to September 2022. Non-probability consecutive sampling technique used. Both genders between 20-60 years of age critically ill patients with acute medical conditions (less than three months duration) or chronic medical condition (more than three months duration) admitted in Sheikh Zayed hospital's intensive care units (Emergency ICU, Neuro ICU, COVID ICU) with serum albumin level <3.5 g/dl were included in present study. Hypoalbuminemia due to any medical condition such as hepatic cirrhosis, nephrotic syndrome, heart failure, acute or chronic inflammatory responses was noted. Samples of critically ill patients with albumin level >3.5g/dl and with visible hemolysis, icterus, lipemia were excluded. Data was collected after taking ethical approval. Sample size was calculated by using formula $n=z^2 \times p(1-p)/\mathcal{E}^2$. where z is z score. $\mathcal{E}$ is the margin of error. N is population size and *p* is proportion of population. By using 95% confidence interval, margin of error 5%, z score value is 1.96 for 95% confidence interval and proportion of population was taken as 46.5% (on the basis of a study conducted, prevalence of hypoalbuminemia in hospitalized patients was calculated as 46.5%).[16] On the basis of this data, sample size of 383 was calculated which was rounded to 408. A total of 408 subjects satisfying the inclusion criteria were included and informed consent was taken. Samples were evaluated for serum sodium level by direct and indirect ion selective electrode methods. Serum sodium measurements by direct ISE method performed on electrolyte analyzer (Electalyte 500) while indirect ISE has been performed on automated chemistry analyzer Atellica CH-930. Other variables like serum cholesterol and triglyceride were also measured for these samples. Data was collected on a predesigned proforma and was entered and analyzed using SPSS Software version 23. Mean difference of serum sodium level by both methods (direct and indirect ISE) were compared by using paired sample t-test. Quantitative variables such as age, duration of illness, duration of hospital stay, serum albumin, serum cholesterol and serum triglyceride were presented in terms of mean±SD. Frequency and percentage were reported for qualitative variables such as gender, residence (urban/rural), chronic liver disease, chronic kidney disease, congestive cardiac failure, malnutrition, inflammatory condition and other significant illness. Confounding factors such as duration of illness, serum albumin levels, serum cholesterol and serum triglyceride, chronic conditions such as chronic liver disease, chronic kidney disease, congestive cardiac failure, inflammatory conditions and malnutrition were controlled through stratification and post stratification independent sample t-test applied to evaluate the statistically significant difference between two groups. p value ≤0.05 taken as significant.

The ethical approval was obtained from the Institutional Review Board of Sheikh Zayed Medical College/ Hospital, Rahim Yar Khan vide letter no. 223/IRB/SZMC/SZH.

Results

Mean age of the total 408 study subjects was 44.86±10.51years with 136 (33.33%) subjects included in 20-40 years age subgroup while 272 (66.66%) were included in 41-60 years age subgroup (Table-1). Distribution of study subjects with respect to other quantitative variables such as duration of illness, duration of hospital stay, serum cholesterol, serum triglyceride and serum albumin is shown in Table-1.

Of the total 408 study subjects, 232 (56.86%) were male while 176(43.13%) were females (Table-2). Distribution of study subjects with respect to other qualitative variables such as residence, chronic liver disease, chronic kidney disease, congestive cardiac failure, inflammatory condition, malnutrition and other significant illness is shown in Table-2.

Mean serum sodium level measured by direct ISE was 137.00±12.187 mmol/L while measured by indirect ISE was 141.22±12.462 mmol/L (Table-3). Mean difference between the two methods (Indirect ISE-Direct ISE) was 4.216±3.517 mmol/L with statistically significant difference (p value <0.05) (Table-4). Mean difference of serum sodium level (Indirect ISE-Direct ISE) in age subgroup 20-40 years (n=136) was 4.12±2.848 mmol/L and in subgroup 41-60 years (n=272), mean difference was 4.24±3.901 with no statistically significant difference (p value: 0.913) Table 4. Mean difference of serum sodium level (Indirect ISE-Direct ISE) in males was 4.10±4.047mmol/L and in females was 4.32±2.868 mmol/L with no statistically significant difference (p value: 0.833) Table-4). Mean difference of serum sodium level (Indirect ISE-Direct ISE) in urban subjects (n=248) was 4.58±2.527 mmol/L and in rural subjects (n=160) was 3.60±4.751mmol/L with no statistically significant difference (p value: 0.341) Table-4. Statistically significant difference of mean serum sodium level with respect to serum triglyceride was observed (p value: 0.026) Table-4. No statistically significant difference of mean serum sodium level was found with respect to duration of illness, duration of hospital stay, serum cholesterol, serum albumin, chronic liver disease, chronic kidney disease, congestive cardiac failure and inflammatory condition.as illustrated in Table-4.

Discussion

Mean serum sodium level measured by direct ISE was 137.00±12.187 mmol/L while measured by indirect ISE was 141.22±12.462 mmol/L (Table-3). Mean difference between the two methods (Indirect ISE-Direct ISE) was 4.216±3.517 mmol/L with statistically significant difference (p value: 0.000) (Table-3). Of the total 408 study subjects, 136 (33.3%) were between 20-40 years age and 272 (66.7%) were between 41-60 years age. Mean age was 44.86±10.51 years (Table-1). Mean difference of serum sodium (Indirect ISE-Direct ISE) in age subgroup 20-40 years was 4.12±2.848 mmol/L while in subgroup 41-60 years was 4.24±3.901 mmol/L. Mean difference of sodium results with respect to age was not statistically significant (p value: 0.913) (Table-4). Of the total

Table 1: Table 1: Distribution of study subjects with respect to Age, Duration of illness, Duration of hospital stay, Serum Cholestrol, Serum Triglyceride and hypoalbuminenia. (n=408)

Variable	*Mean±SD*	*Subgroups*	*Frequency*	*Percentage (%)*
Age (Years)	44.86±10.51	20-40	136	33.3
		41-60	272	66.7
		Total	408	100
Duration of illness (days)	74.16±44.208	≤3 months	176	43.1
		>3 months	232	56.9
		Total	408	100
Duration of hospital Stay (days)	7.71±3.36	≤5 days	56	13.7
		5-10 days	288	70.6
		>10days	64	15.7
		Total	408	100
Serum Cholestrol (mg/dl)	155.84±45.30	<100	24	5.9
		100-150	184	45.1
		151-200	96	23.5
		>200	104	25.5
		Total	408	100
Serum Triglyceride (mg/dl)	143.47±51.010	<100	72	17.6
		100-150	200	49.0
		151-200	80	19.6
		>200	56	13.7
		Total	408	100
Hypoalbuminemia (g/dl)	2.543±0.446	<2.0	64	15.7
		2.0-2.5	112	27.5
		2.6-3.0	176	43.1
		3.1-3.5	56	13.7
		Total	408	100

Table 2: Distribution of study subjects with respect to Gender, Residence, CKD, CLD,CCF, inflammatory condition. (n=408)

Variable	*Subgroups*	*Frequency*	*Percentage (%)*
Gender	Male	232	56.9
	Female	176	43.1
	Total	408	100
Residence	Urban	248	60.8
	Rural	160	39.2
	Total	408	100
CKD	Yes	136	33.3
	No	272	66.7
	Total	408	100
CLD	Yes	136	33.3
	No	272	66.7
	Total	408	100
CCF	Yes	48	11.8
	No	360	88.2
	Total	408	100
Inflammatory condition	Yes	200	49.0
	No	208	51.0
	Total	408	100

408 study subjects, 232 (56.86%) were male while 176 (43.13%) were females (Table-2). Mean difference of serum sodium (Indirect ISE- Direct ISE) in males was 4.10±4.047 mmol/L while in females was 4.32±2.868 mmol/L. Mean difference of sodium results was not statistically significant with respect to gender (*p* value: 0.833) (Table 4).

According to CLIA requirement for acceptable performance, total allowable error for sodium measurement is 4 mmol/L.[17] The findings of our study are consistent with a study conducted by Refardt J. et al and it was found that mean serum sodium level measured by indirect ISE ranged from 141±2.9 mmol/L to 151±2.1mmol/L while measured by direct ISE was 140±3mmol/L to 149±2.8 mmol/L with statistically significant difference between two groups (*p* value <0.001).[18] Another study conducted by Story D. et al showed that mean serum sodium measured by direct ISE was 139 mmol/L while measured by indirect ISE was 141 mmol/L. Mean difference of serum sodium was 2.1 mmol/L and statistically significant and results are consistent with our findings. 13% of central laboratory sodium results shows pseudonormonatremia and 7% of central laboratory results shows pseudohyernatremia.[19] Zamanabadi et al., demonstrated in their study that the mean sodium level from blood gas analyzer based on direct ISE was 138.38±6.026 mEq/L and laboratory analyzer based on indirect ISE was 137.42±4.413 mmol/L. The mean difference in sodium levels between two methods was significantly different (*p* value = 0.007). The difference of mean sodium level between two methods was consistent with our study findings.[20] Mean serum sodium level measured by direct ISE in age subgroup >60 years was

Table 3: Mean serum sodium level (Na) in mmol/L measured by Direct ion selective electrode (DISE) and Indirect ion selective electrode (Indirect ISE) and mean difference of serum sodium level (Indirect-Direct ISE) in mmol/L. (N=408)

Method	*Mean Na (mmol/L)*	*N*	*Std Deviation*	*Std Error Mean*	*p value*
Indirect ISE	141.22	408	12.462	1.745	
Direct ISE	137.00	408	12.187	1.707	0.000
Indirect-Direct ISE	4.216	408	3.517	0.493	

Paired Samples Statistics

Table 4: Mean difference of serum sodium level (mmol/L) measured by direct and Indirect ISE with respect to different variables. (n=408)

Variable	*Subgroups*	*Difference (Indirect-Direct) ISE (mmol/L)*		*p Value*
		Mean	*SD*	
Age (Years)	20-40	4.12	2.848	0.913
	41-60	4.24	3.901	
Gender	Male	4.10	4.047	0.833
	Female	4.32	2.868	
Residence	Urban	4.58	2.527	0.341
	Rural	3.60	4.751	
Duration of illness	≤3 months	3.73	2.434	0.418
	>3 months	4.55	4.222	
Duration of hospital stay	≤5 days	3.65	4.197	0.441
	>5 days	4.47	3.221	
Serum cholestrol (mg/dl)	≤200	4.42	3.666	0.445
	>200	3.54	3.256	
Serum triglyceride (mg/dl)	≤150	4.97	2.702	0.026
	>150	2.65	4.541	
Serum albumin (g/dl)	≤2.5	5.00	3.941	0.162
	>2.5	3.59	3.541	
CKD	Yes	4.12	4.807	0.913
	No	4.24	2.818	
CLD	Yes	5.00	3.725	0.258
	No	3.79	3.453	
CCF	Yes	3.50	3.50	0.615
	No	4.29	3.678	
Inflammatory condition	Yes	4.76	3.192	0.271
	No	3.65	3.857	

138.18±7.256 while measured by indirect ISE was 137.09±5.405 mmol/L with statistically significant difference (*p* value: 0.02). In age subgroup ≤60 years, mean serum sodium level between direct and indirect ISE was statistically significant (*p* value: 0.039). Our findings do not indicate the significant difference between two methods with respect to age.[20]

Mean serum sodium level with respect to gender between direct and indirect ISE was statistically significant (*p* <0.05). In male, mean sodium level measured by direct and indirect ISE was significant with p value: 0.025 while in females, *p* value was 0.03. The difference between two methods with respect to gender was not consistent with our study findings.[21]

A similar study conducted by Solak et al., suggested that blood gas analyzers which are based on direct ISE tend to underestimate the serum sodium level when compared with automated chemistry analyzers based on indirect ISE regardless of their absolute serum sodium level in the blood. The study does not account for potential variations between the two methods for measuring serum sodium level.[21]

Of the total 408 study subjects, 176(43.13%) were having ≤3 months duration of illness and 232 (56.86%) having >3months duration of illness with mean duration of illness 74.16±44.208 days (Table 1) Mean difference of serum sodium (Indirect ISE- Direct ISE) in ≤3 months duration of illness subgroup was 3.73±2.434 mmol/L while in >3months duration of illness was 4.55±4.222 mmol/L with statistically non-significant difference between two groups (*p* value: 0.418) (Table-4).

Of the total 408 study subjects, 56 (43.13%) were having ≤5days duration of hospital stay while 352 (56.86%) were having >5 days duration of hospital stay with mean duration of hospital stay 7.71±3.366 days (Table-1). Mean difference of serum sodium (Indirect ISE- Direct ISE) in ≤5 days duration of hospital stay subgroup was 3.65±4.1974 mmol/L while in >5 days subgroup was 4.47±3.221 mmol/L with statistically non-significant difference between two subgroups (*p* value: 0.441) (Table-4). No significant data available demonstrating the effect of mean difference of serum sodium level measured by direct and indirect ISE with respect to duration of illness and duration of hospital stay. Of the total 408 study subjects, 176 (43.13%) were having serum albumin ≤2.5 g/dl while 232 (56.86%) were having serum albumin >2.5g/dl with mean serum albumin level 2.543±0.446g/dl (Table-1). Mean difference of serum sodium (Indirect ISE-Direct ISE) in subgroup ≤2.5g/dl serum albumin was 5.00±3.491 mmol/L while in >2.5 g/dl serum albumin subgroup was 3.59±3.541 mmol/L with statistically non-significant difference between two groups (*p* value: 0.162) (Table-4). Chopra et al., demonstrated in their study that there is statistically significant difference between direct and indirect ISE with respect to protein subgroups (*p* value: 0.005).[22]

Of the total 408 study subjects, 304 (74.50%) were having serum cholesterol ≤200 mg/dl while 104(25.49%) were having serum cholesterol >200mg/dl with mean serum cholesterol level 155.84±45.300 mg/dl (Table-1). Mean difference of serum sodium (Indirect ISE-Direct ISE) in subgroup ≤200 mg/dl serum cholesterol was 4.42±3.666 mmol/L while in >200 mg/dl serum cholesterol subgroup was 3.54±3.256 mmol/L with statistically non-significant difference between two groups (*p* value: 0.445) (Table-4). The difference of serum sodium measured by direct and indirect ISE in cholesterol subgroup <150 mg/dl was 6.6±4.5 mmol/L while in subgroup >150mg/dl was 4.2±4.3 mmol/L. 59% samples in subgroup <150mg/dl and 47.2% of samples in >150mg/dl subgroup shows difference of mean serum sodium >5mmol/L which is statistically significant.[22]

Of the total 408 study subjects, 272(66.66%) were having serum triglyceride ≤150 mg/dl while 136 (50.98%) were having serum triglyceride >150 mg/dl with mean serum triglyceride level 143.47±51.010 mg/dl (Table-1). Mean difference of serum sodium (Indirect ISE-Direct ISE) in subgroup ≤150 mg/dl serum triglyceride was 4.97±2.702 mmol/L while in >150 mg/dl serum triglyceride subgroup was 2.65±4.541 mmol/L with statistically significant difference between two groups (*p* value: 0.026) (Table-4). Chopra et al., demonstrated in their study that mean difference of serum sodium results in TG subgroup <150mg/dl was 5.0±4.6 mmol/L while in TG subgroup >150 md/dl, mean difference was 6.0±4.7 mmol/L. No statistically significant difference between two groups was demonstrated. No difference of mean serum sodium level evaluated by controlling potential confounding factors in this study.[22] Dimeski et al., have demonstrated in their study that increase in lipid concentration can falsely decrease the serum electrolytes due to electrolyte exclusion effect measured by indirect ISE. For every 10 mmol/L increase in lipid concentration results in decrease of 1mmol/L serum sodium.[23]

Our study had certain limitations, it was a single centered study. Discrepancy of sodium results were not evaluated for subjects without having critical illness and inter method agreement was not studied using Bland Altman plot and Pearson correlation coefficient. On the basis of our study, it is concluded that direct ISE should be preferred method for estimation of serum sodium level in hypoalbuminemia patients but there are some disadvantages of using this method. There is decrease throughput of test in analyzers based on direct ISE and it also increased the turnaround time but no such disadvantages are observed in analyzers based on Indirect ISE as most of the automated chemistry analyzers are based on Indirect ISE which are having major advantage of ease of operation as well as cost effectiveness. Less sample volume is used and measurable concentration range is increased. Multiple samples are analyzed simultaneously for multiple parameters hence throughput is improved.

It is recommended that intra individual difference of serum sodium level between two methods should also be evaluated in the absence of acute illness so that false decisions can be avoided in every patient with hypoalbuminemia.

The results of serum sodium level measured by direct and indirect ion selective electrode (ISE) are not comparable in critically ill patients with hypoalbuminemia and difference between two methods was found statistically significant. Interchangeable use of direct and indirect ISE methods should be avoided, especially in the setting of hypoalbuminemia. As, the results of serum sodium level measured by indirect ISE are misleading in the setting of hypoalbuminemia and critically ill patients can be misdiagnosed and mismanaged. Lab staff should be made aware of the discrepant results of serum sodium measured by indirect ISE in hypoalbuminemia and therefore direct ISE method should be used preferably in the setting of hypoalbuminemia. Standardization should be considered by hospital laboratories to use direct ISE for serum sodium measurement.

Conflict of interest: None declared.

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