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Original Article

Comparing the effect of Hypoalbuminemia on Sodium measured by Indirect versus Direct Ion Selective Electrode Method

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ABSTRACT

Objective: To evaluate the effect of low serum Albumin levels on serum sodium measurement when analyzed by the indirect Ion Selective Electrode (ISE) method and to compare the results with the direct Ion selective electrode (ISE) method.
Study Design: Cross-sectional study
Place and Duration of Study: Department of Chemical Pathology, Armed Forces Institute of Pathology, Rawalpindi Pakistan, from Jan to Mar 2021.
Methodology: Patients of either gender, aged 18 to 70 years, who were admitted to the Intensive Care Unit of Combined Military Hospital, Rawalpindi, were selected. A total of 200 blood samples were collected in a gel tube. Serum samples were analyzed for albumin and sodium within two hours of sample collection. Sodium levels were measured concurrently by both direct and indirect ISE methods. The difference in results between these two techniques was studied.
Results: Hypoalbuminemia was detected in 176(88%) patients, while 24(12%) had normal albumin levels. In Hypoalbuminemic patients, serum sodium measurements were higher using the indirect ISE method (134.07±5.55) compared to the direct ISE method (130.95±6.04); the difference between the two techniques was statistically significant (p-value <0.001). Pearson correlation coefficient (r-value = -0.86, p-value <0.001) revealed a symmetrical increase in differences between the two methods as the albumin level decreased.
Conclusion: In Hypoalbuminemic patients, the indirect ISE method gave falsely raised results of serum sodium. In such patients, serum sodium measurement by the Direct ISE method offers more accurate and consistent electrolyte results.

Keywords: Hypoalbuminemia, Ion selective electrode (ISE), Serum sodium measurement.

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INTRODUCTION

Albumin is a predominant plasma protein in circulation, mainly synthesized in the liver. It plays a vital role in regulating the distribution of body fluid and maintaining acid-base physiology and is an essential transport protein of the body.[1] Serum albumin concentration <35g/L is taken as hypoalbuminemia. It is amongst the most important findings in critically ill patients and a predictor of nutritional status and disease severity in such patients.[2,3,4]

Abnormal serum sodium level is another common finding in hospitalized patients.[5,6] Flame photometry was later replaced by the Ion Selective Electrode (ISE) method, which provided more reliable results of the plasma sodium concentration.[7]

The ISE method uses two electrodes: the reference electrode with constant potential and the ion-specific electrode. The potential difference between the two electrodes is used to measure the concentration of sodium using Nernst Equation.[8] There are two popularly known methods. In the indirect ISE method, the sample dilution is done with a fixed volume of diluent assuming that plasma consists of 7% dissolved solid and 93% water. Whereas the direct ISE method directly measures the activity of ions without sample dilution.[9] In the case of hyper-proteinemia, there is an increase in the solid phase and a reduction in the liquid phase of plasma. By the indirect ISE method, diluting the reduced liquid phase by a fixed amount of diluent will lead to falsely low sodium measurement phenomena well recognized as the electrolyte exclusion effect.[10] On the contrary, such variations do not affect direct ISE output. Less is known about whether hypopro-teinemia or hypoalbuminemia can cause false high sodium levels when measured by the indirect ISE method. The serum sodium level is a frequently advised test in hospitalized patients, and most automated chemistry analyzers use the indirect ISE method to estimate electrolytes. As Hypoalbuminemia is a common finding in hospitalized patients, to avoid any erroneous reporting by indirect ISE method, the study was conducted to determine the effect of

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hypoalbuminemia on indirect ISE-measured sodium considering direct ISE as the gold standard.

METHODOLOGY

The cross-sectional study was conducted at the Department of Chemical Pathology, Armed Forces Institute of Pathology, Rawalpindi, over three months from January to March 2021 after approval from the Institute Ethical Committee (FC-CHP19-18/READ-IRB/21/143). The sample size was calculated by the WHO sample size calculator taking 15% as the prevalence of hypoalbuminemia in hospitalized patients.[11]

Inclusion Criteria: Samples of critically ill patients admitted to the intensive care unit of Combined Military Hospital (CMH), Rawalpindi, with various ailments, were collected using a nonprobability consecutive sampling technique.

Exclusion Criteria: samples with insufficient volume, Hemolyzed, Icteric and Lipemic samples were also excluded from the study.

After taking informed written consent, 3 ml of blood sample was collected in a gel tube. Samples centrifugation was done at 3500 rpm for 3 minutes. Serum was separated and analyzed within two hours of collection. Samples were analyzed for serum albumin and sodium levels simultaneously. Both direct & indirect ISE methods measured serum sodium. Serum albumin and serum sodium by the Indirect ISE method were analyzed on an automated chemistry analyzer ADVIA 1800 (Siemens). At the same time, serum sodium by direct ISE method was analyzed on Cobas b 221 blood gas analyzer. Controls were run on all the instruments and plotted on the LJ chart before analysis.The albumin level was divided into six groups, i.e. <15g/L, 15-19g/L, 20-24g/L, 25-29g/L, 30-34g/L, and >35g/L.[12] The mean and SD of the difference between sodium levels measured by Indirect and Direct ISE in each group were calculated. For detecting serum abnormalities, the reference interval of sodium was set to be between 135 and 150 mmol/L, and for albumin was 35-50 g/L.[13]

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Results were expressed as mean±SD. A mean comparison of Indirect versus Direct ISE-measured sodium levels in patients was made by paired t-test, and the *p*-value of ≤0.05 was taken as statistically significant. Pearson correlation was used to determine the correlation between albumin levels and the difference between Indirect versus Direct ISE-measured sodium levels.

RESULTS

A total of 200 samples were included in the study, out of which 130(65%) were male while 70(35%) were females. The mean age of patients was 56.97± 14.99 years. Hypoalbuminemia (serum albumin <35g/L) was present in 176(88%) of patients, while 24(12%) had normal serum albumin levels. The mean and SD of serum sodium levels measured by both direct and indirect ISE was compared in patients with low albumin levels (<35g/L) and normal albumin level (35-50 g/L), as shown in Table-I.

Table-I: Comparison of sodium levels by Direct and Indirect ISE Method in Hypo-albuminemic and Normo-albuminemic Patients (n=200)

	Na+Indirect ISE (Mean±SD)	Na+Direct ISE (Mean±SD)	*p*-value
Low Serum Albumin <35 g/L (n=176)	134.07±5.55	130.95±6.04	<0.01
Nor Serum Albumin 35-50 g/L (n=24)	135.04±4.90	134.96±4.90	0.664

There was a statistically significant difference in sodium level measured by indirect and direct ISE methods in hypoalbuminemia patients with a *p*-value <0.001. Using serum albumin levels, patients were divided into six groups. The mean difference of sodium measured by indirect and direct ISE methods in each group was calculated. For an increased albumin level, there was not much difference between the values of sodium by the two methods. The difference was greatest when serum albumin was less than 15 g/L. The results of electrolyte analysis are shown in Table-II.

Table-II: Mean difference of Indirect and Direct ISE Measured Sodium in Different Albumin Groups (n=200)

Serum Albumin Level (g/L)	Difference of Indirect vs direct ISE measured Na+(mmol/L)
	(Mean±SD)
35-45 (n=24)	0.08±0.92
30-34 (n=54)	1.38±0.94
25-29 (n=51)	2.90±1.13
20-24 (n=46)	4.23±0.82
15-19 (n=19)	4.94±0.84
<15 (n=6)	5.33±1.03

Pearson correlation between the albumin concentration and the difference between the indirect and direct ISE measured sodium showed a significant negative linear correlation (r-value=-0.86, *p*-value <0.01), as shown in Figure.

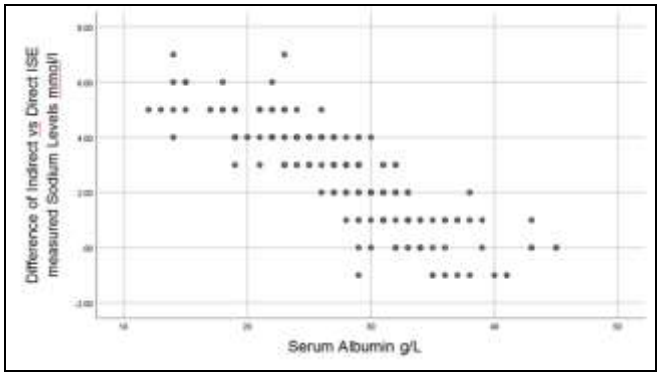

Figure: Correlation Analysis Between serum Albumin & Difference of Indirect versus Direct ISE Measured Sodium Levels

DISCUSSION

Through results, it was concluded that 176(88%) of the patients suffered from hypoalbuminemia. The indirect ISE method misclassified 38(19%) cases as pseudonormonatremia. Patients were hyponatremic, but indirect ISE categorized the patients as normonatremic. However, only 1(0.5%) of the case showed pseudo-hypernatremia on the indirect ISE method. Hence, the indirect ISE method gave false high results of serum sodium in hypoalbuminemia patients.

In a retrospective study 46.5% of hospitalized patients were hypoalbuminemia.[12] The major finding of our research was the detection of positive bias in serum sodium levels when measured by the Indirect ISE method in hypoalbuminemia patients. These findings were consistent with previous studies.[12-14]

According to Clinical Laboratory Improvement Amendments (CLIA), the total allowable error for performing serum sodium is ± 4 mmol/l.[15] Our study concluded that there was an increase in the difference between indirect versus direct ISE-measured serum sodium as the level of albumin decreased in the sample. The same findings were demonstrated by Story *et al*. [16] The mean difference of more than four mmol/L was found in patients with serum albumin levels less than 25g/L. Stove *et al*.[17] in a prospective cohort study conducted on 4006 patients, also demonstrated a significant negative linear correlation between indirect ISE-measured sodium and direct ISE-measured sodium relative to changes in total protein concentration, concluding that with the decrease of 10g/L in total protein concentration, there is the increase of 1.3mmol/L in Indirect ISE measured sodium results.

The indirect ISE method is commonly used in automated chemistry analyzers. The main advantage is the ease of operation and cost-effectiveness; multiple tests can be performed simultaneously from a single sample hence improving the throughput and the predilution of the sample leads to the usage of less sample volume while expanding the measurable concentration range. However, the main disadvantage of the Indirect ISE method is its impact on results due to variations in plasma albumin or proteins.[10] These findings were also evident in our study. In contrast, Direct ISE is a common method in blood gas analyzers, and other point-of-care instruments have the advantage that they are unaffected by such variations in plasma proteins or albumin levels hence providing true estimates of serum sodium levels.[18] As every sample has to be run separately, the disadvantage of the Direct ISE method is that it reduces the throughput the test & increases the turnaround time.

Indirect ISE-measured sodium in hypoalbuminemia patients may be misleading and lead to ineffective treatment of critically ill patients. Therefore, It is recommended that measurement of serum sodium levels, especially in patients with albumin levels <25 g/L, should be done by direct ISE method to get accurate results.

CONCLUSION

The majority of patients admitted to the Intensive Care Unit were hypoalbuminemia. The indirect ISE method gave falsely raised serum sodium results in hypoalbuminemia patients. The difference between the two methods was more than CLIA acceptable limit (4 mmol/l) in patients with albumin levels <25g/l. Therefore, serum sodium levels of such patients should be performed by direct ISE methods. Furthermore, lab staff should be made aware of the effect of albumin on sodium measurement by the indirect ISE method.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AIP & ZHH: Conception, study design, drafting the manuscript, approval of the final version to be published.

MA & SB: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

AB & HJ: Data acquisition, data analysis, data inter-pretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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