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Research Article

Comparison of Direct and Indirect Ion-Selective Electrode-Based Methods for Serum Electrolyte Estimation: A Retrospective Study

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Abstract

Background and Objectives: Sodium and Potassium are the most investigated analytes in the routine clinical chemistry laboratories from different clinical departments. The measurement of serum electrolytes, i.e. sodium (Na^+) and potassium (K^+) of patients are crucial for clinical decision making. Nowadays, electrolyte analyzers use ion-selective electrode (ISE) based technologies which include: direct (dISE) and indirect (iISE). The iISE targets clinical laboratories while dISE serves at point-of-care settings. We mapped this study to evaluate the serum Na^+ and serum K^+ levels by both iISE and dISE methods and to correlate these values with serum total protein and serum albumin levels.

Methods: In this retrospective study, we analyzed the serum electrolytes and protein values of 348 patients. We juxtaposed the serum Na^+ and serum K^+ levels assessed through the direct (dISE) and indirect (iISE) methods. We also contrasted these values for the female and male participants with their serum total protein (TP) and serum albumin levels. The Shapiro-Wilk test was employed to determine the normality of the data distribution. We also correlated the obtained data for both direct (dISE) and indirect (iISE) methods. R software (version 4.4.1) was used for the data analysis.

Results: Out of 348 patients we analyzed, 110 (31.6%) were females. The median age of the study population was 54.0 (39.0-65.0) years. The median serum Na^+ and serum K^+ values of the study population were 139.0 (135.0-142.0) mEq/L and 4.4 (4.0-5.1) mEq/L, respectively. The median serum total protein and albumin levels of the study population were 6.8 (5.7-7.2) g/dL and 4.0 (2.9-4.3) g/dL, respectively. Our analysis revealed positive associations among the serum electrolytes and protein values.

Conclusion: We found that both direct (dISE) and indirect (iISE) methods can be used interchangeably for the estimation of serum Na^+ and serum K^+ levels. The correlation plots indicated that direct (dISE) method is more favorable than the indirect (iISE) method. However, the associations were not statistically significant.

Keywords: *Serum Electrolyte; Albumin; Total Protein; Beckman Coulter; Correlation*

Abbreviations

dISE: Direct Ion-Selective Electrode-Based Method; EEF: Electrolyte Exclusion Effect; iISE: Indirect Ion-Selective Electrode-Based Method; ISE: Ion-Selective Electrode; IQR: Interquartile Range

Introduction

The sodium homeostasis in range of 136-145 mEq/L is required for retention of fluid in vascular compartments. Hyponatremia with serum sodium level (125-135 mEq/L), can lead to varied presentation. Manifestation of hyponatremia largely depends on the level to which sodium has fallen and the rate of decrease [1]. Mild hyponatraemic subjects are mostly asymptomatic and moderate hyponatremia have cognition difficulties, whereas acute onset of hyponatremia with onset < 48 hrs and severe hyponatraemic subjects with sodium < 120 mEq/L have fluid in extravascular space can lead to cell swelling, cerebral edema, noncardiogenic pulmonary edema, respiratory distress, seizure, convulsion, and coma [2,3].

Guidelines used for classification of severity of electrolyte disturbances are based on measurement of electrolyte by using ion selective method (ISE). More than 99% of the present-day laboratories use two variant ion-selective electrode (ISE) based technologies for electrolyte estimation, which include direct (dISE) and indirect (iISE) [4,5]. The dISE method serves at point-of-care setting, blood gas analyzer which uses heparinized whole blood, and dry chemistry analyzer which use serum samples for electrolyte estimation [6]. Contrarily, the iISE method uses a fixed predilution step with diluent in the ratio of 1:20 to 1:34 depending on the analyte [7,8]. The major variation between two methods for electrolyte estimation is that, dISE neither required any predilution of serum nor affected by solid phase of the sample [3,6]. Many laboratories currently use iISE as a popular method for estimating electrolytes. This necessitates dilution of smaller sample volumes to be perform multiple analysis simultaneously [9].

Plasma volume consists of water and total solids (primarily protein and lipid). In an aliquot of plasma, total solid contributes approximately 7% and rest 93% of plasma volume is actually water and the main electrolytes (Na^+, K^+, Cl^-, $HCO3^-$) confined to the water phase [10]. Both direct and indirect ISE measures electrolyte activities in plasma water, but final result of electrolyte concentration is reported from total plasma, assuming normal solid phase [8,10].

In a fixed volume of total plasma (10 μL) when goes for analysis of electrolyte by iISE method, only 9.3 μL of plasma water that contains the electrolyte is added to the diluent but the concentration of Na^+ determined by indirect ISE is calculated from total plasma volume, not from plasma water volume. This negative error arises from the assumption that volume fraction of water in total plasma was constant and this difference could be ignored. All the reference ranges of electrolytes used in clinical practice are based on the presumption and actually reflect concentration and related to total plasma volume rather than to water volume [11]. The electrolyte exclusion effect (EEF) describes the exclusion of electrolytes or decrease in the concentrations of electrolytes from fraction of total plasma volume that is occupied by solids. EEF becomes troublesome in case of hyperlipidaemia and hyperproteinaemia. In these settings, falsely low electrolyte values are obtained whenever samples are diluted before analysis [9]. Hypoproteinaemia also affects the electrolyte estimation [9,11].

Many laboratories receive samples of electrolytes for continuous monitoring. Hence, there exists a possibility of evaluating both direct and indirect ISE methods in the same patient. This confuses clinical decision making, introduces dilemma in the treatment of dyselectrolytemia. Therefore, our study aims to evaluate the serum Na^+ and serum K^+ levels by both iISE and dISE methods and to correlate these values with serum total protein and serum albumin levels.

Materials and Methods

This retrospective study was conducted at Kalinga Institute of Medical Sciences, India. Before commencing the study, we obtained the ethics approval from the concerned authority (KIIT/KIMS/IEC/1875/2024 dated 17/07/2024). We assessed the data from January to June 2024.

Our study included patients of either gender whose serum electrolytes had been checked with both dISE and iISE methods. The subjects who were on intravenous infusion were excluded from the study. The hemolyzed, icteric, lipemic samples, samples from operating theatres, and repeat samples from the same individual were excluded from the study.

Under strict aseptic measures, a 2 mL venous blood specimen were collected from the medial cubital vein in red-top vacutainer and allowed to clot at room temperature. After centrifuging at 3000 rpm for 10 minutes, separated serum samples were analysed for total protein, albumin, Na^+ and K^+. All the parameters were analysed by modular system auto analyser. Serum Na^+ and K^+ were measured by both indirect ISE (Beckman coulter AU400) and direct ISE (OCD 5600) analyser within 2 hours of collection. Total protein was measured by biuret method, albumin by bromocresol green (BCG) and globulin was calculated.

For this retrospective study, we adopted convenience sampling. We used the Shapiro-Wilk test to ensure that the collected data were normally distributed. For categorical variables, frequency and proportion were used as summary statistics. The continuous data was presented using the median and interquartile range (IQR). We used Pearson's chi-square test to compare various traits. For data analysis, we used R software (version 4.4.1) [14]. The statistical tests were two-tailed. The p-values less than 0.05 were interpreted as statistically significant.

Results

We analyzed blood samples of 348 patients. Of them, 110 (31.6%) were females. The median age of the study population was 54.0 (39.0-65.0) years [female: 52.0 (38.0-60.0) years; male: 56.0 (40.0-67.0) years; p = 0.17]. The median serum Na^+ of the study population was 139.0 (135.0-142.0) mEq/L [female: 139.0 (135.8-142.0) mEq/L; male: 138.0 (134.8-142.0) mEq/L; p = 0.77]. The median serum K^+ of the study population was 4.4 (4.0-5.1) mEq/L [female: 4.5 (4.0-5.3) mEq/L; male: 4.4 (3.9-5.0) mEq/L; p = 0.41]. The median serum total protein level of the study population was 6.8 (5.7-7.2) g/dL [female: 6.8 (5.8-7.3) g/dL; male: 6.8 (5.7-7.2) g/dL; p = 0.64]. The median serum albumin level of the study population was 4.0 (2.9-4.3) g/dL [female: 3.9 (3.1-4.2) g/dL; male: 4.0 (2.8-4.4) g/dL; p = 0.55]. The biochemical parameters and age have been elucidated in table 1.

Parameter	Total (n = 348)	Female (n = 110)	Male (n = 238)	p-value
Age (years)	54.0 (39.0-65.0)	52.0 (38.0-60.0)	56.0 (40.0-67.0)	0.17
Serum Na^+ (mEq/L)	139.0 (135.0-142.0)	139.0 (135.8-142.0)	138.0 (134.8-142.0)	0.77
Serum K^+ (mEq/L)	4.4 (4.0-5.1)	4.5 (4.0-5.3)	4.4 (3.9-5.0)	0.41
Serum total protein (g/dL)	6.8 (5.7-7.2)	6.8 (5.8-7.3)	6.8 (5.7-7.2)	0.64
Serum albumin (g/dL)	4.0 (2.9-4.3)	3.9 (3.1-4.2)	4.0 (2.8-4.4)	0.55

Table 1: *The sociodemographic traits of the study population.*

The continuous data are expressed as median (IQR).

Figure 1 portrays the serum Na^+ of the study participants measured through both methods. The x-axis represents the sodium values assessed with Beckman coulter AU400 analyzer. And, the y-axis expresses the sodium values evaluated through OCD 5600. As per the measurements by Beckman coulter AU400 analyzer, the median serum Na^+ of the study population was 138.0 (135.0-140.0) mEq/L. According to the evaluations by OCD 5600 analyzer, the median serum Na^+ of the study population was 140.0 (135.0-143.0) mEq/L. The scatter plot illustrates that there was a positive correlation ($r = 0.74$, $p < 0.001$) between the serum Na^+ values obtained through dISE and iSE methods.

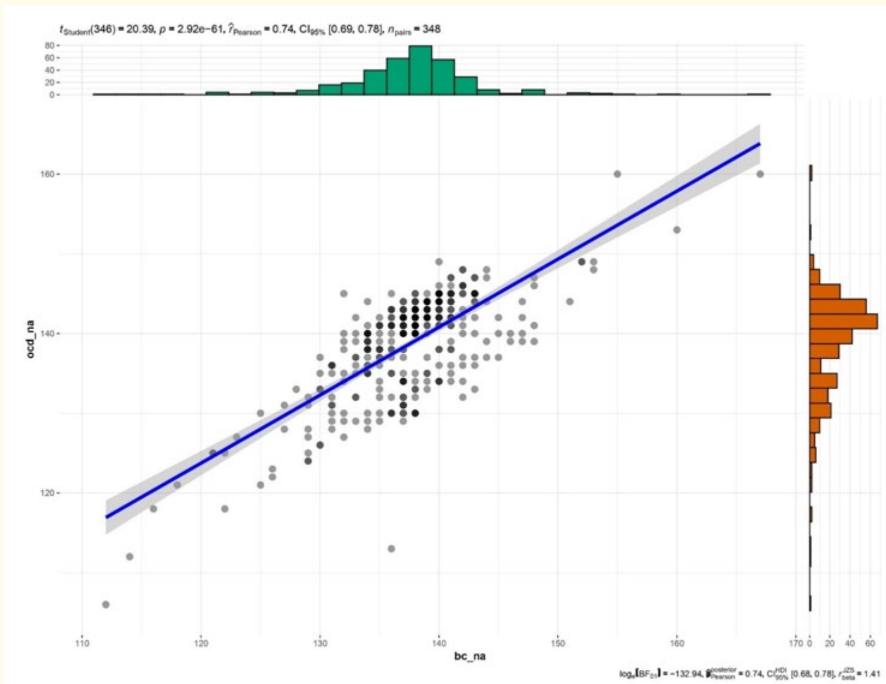

Figure 1: *Comparison of serum Na+ measured by both methods.*

The scatter plot demonstrates the serum sodium values of the study participants. The histograms on x- and y-axes represent the serum sodium values measured through indirect ISE (Beckman coulter AU400) and direct ISE (OCD 5600) analyser, respectively.

Figure 2 portrays the serum K^+ of the study participants measured through both methods. The x-axis represents the potassium values assessed with Beckman coulter AU400 analyzer. And, the y-axis expresses the potassium values evaluated through OCD 5600. As per the measurements by Beckman coulter AU400 analyzer, the median serum K^+ of the study population was 4.2 (3.8-4.6) mEq/L. According to the evaluations by OCD 5600 analyzer, the median serum K^+ of the study population was 4.8 (4.2-5.5) mEq/L. The scatter plot illustrates that there was a positive correlation ($r = 0.75$, $p < 0.001$) between the serum K^+ values obtained through dISE and iISE methods.

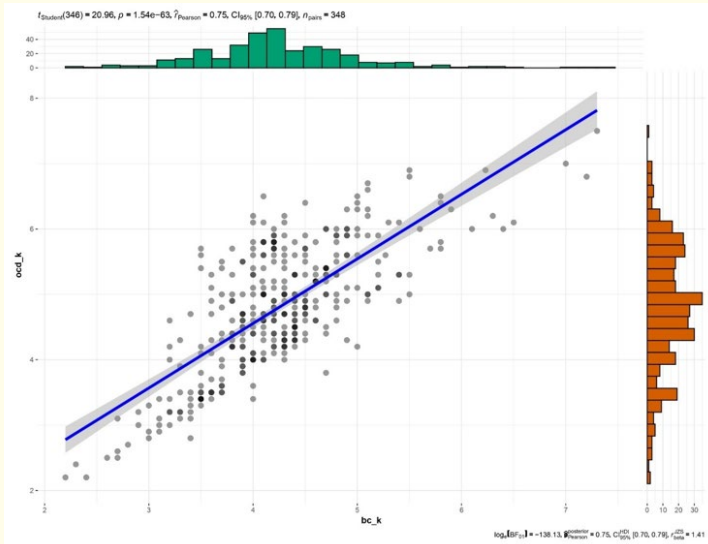

Figure 2: *Comparison of serum K+ measured by both methods.*

The scatter plot demonstrates the serum sodium values of the study participants. The histograms on x- and y-axes represent the serum sodium values measured through indirect ISE (Beckman coulter AU400) and direct ISE (OCD 5600) analyser, respectively.

Figure 3 displays the serum Na^+ of the female and male participants measured through both methods. The x-axis represents the serum total protein values. And, the y-axis expresses the serum Na^+ values. There were positive correlations (female: r = 0.39, p = 0.022; male: r = 0.39, p = 0.023) between the serum Na^+ values obtained through dISE method. However, the values evaluated through iISE method did not have any statistical significance (female: r = -0.09, p = 0.57; male: r = 0.13, p = 0.61) with serum total protein values.

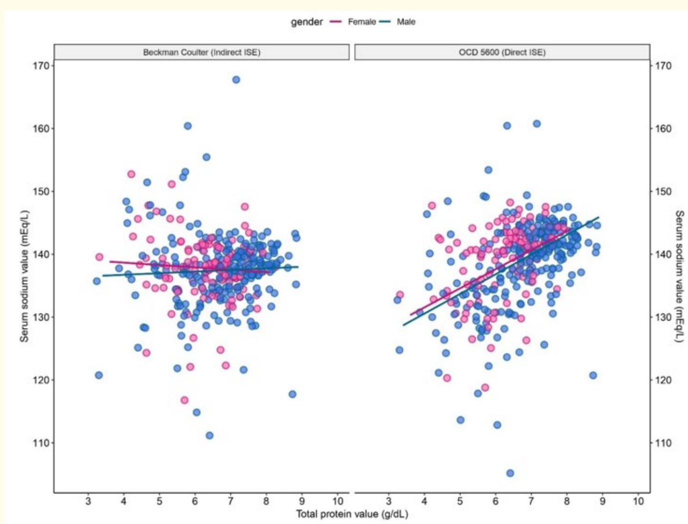

Figure 3: *Association between serum Na+ and serum total protein.*

The scatter plots demonstrate the association of serum Na^+ and serum total protein values of the female and male participants. The subgroup analysis was performed based on the methods of assessment. The regression lines imply the association of these values among female and male participants.

Figure 4 displays the serum K^+ of the female and male participants measured through both methods. The x-axis represents the serum total protein values. And, the y-axis expresses the serum K^+ values. There were positive correlations (female: r = 0.38, p = 0.021; male: r = 0.37, p = 0.020) between the serum K^+ values obtained through dISE method. However, the values evaluated through iISE method did not have any statistical significance (female: r = 0.12, p = 0.36; male: r = 0.21, p = 0.28) with serum total protein values.

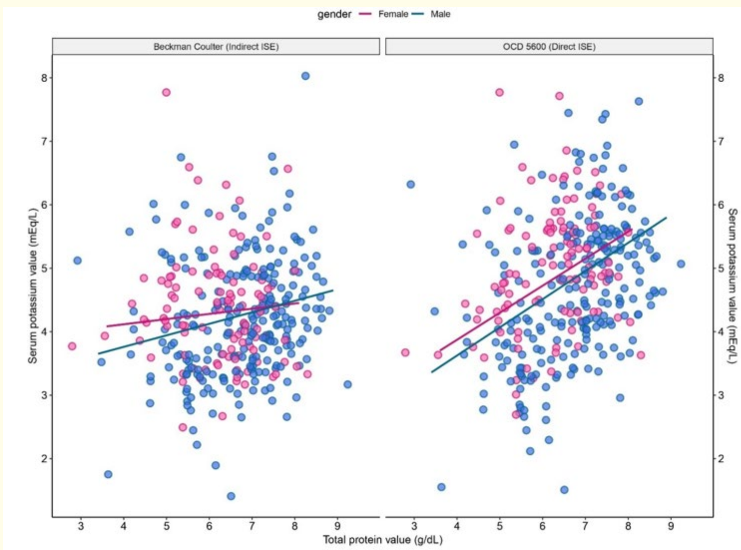

Figure 4: *Association between serum K^+ and serum total protein.*

The scatter plots demonstrate the association of serum K^+ and serum total protein values of the female and male participants. The subgroup analysis was performed based on the methods of assessment. The regression lines imply the association of these values among female and male participants.

Figure 5 displays the serum Na^+ of the female and male participants measured through both methods. The x-axis represents the serum albumin values. And, the y-axis expresses the serum Na^+ values. There were positive correlations (female: r = 0.43, p = 0.019; male: r = 0.41, p = 0.021) between the serum Na^+ values obtained through dISE method. However, the values evaluated through iISE method did not have any statistical significance (female: r = 0.08, p = 0.54; male: r = 0.11, p = 0.58) with serum albumin values.

The scatter plots demonstrate the association of serum Na^+ and serum albumin values of the female and male participants. The subgroup analysis was performed based on the methods of assessment. The regression lines imply the association of these values among female and male participants.

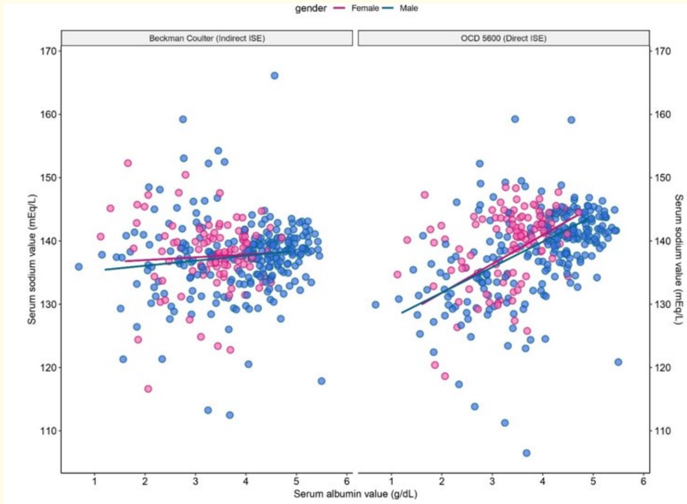

Figure 5: *Association between serum Na^+ and serum albumin.*

Figure 6 displays the serum K^+ of the female and male participants measured through both methods. The x-axis represents the serum albumin values. And, the y-axis expresses the serum K^+ values. There were positive correlations (female: r = 0.39, p = 0.022; male: r = 0.40, p = 0.020) between the serum K^+ values obtained through dISE method. However, the values evaluated through iISE method did not have any statistical significance (female: r = 0.03, p = 0.89; male: r = 0.20, p = 0.64) with serum albumin values.

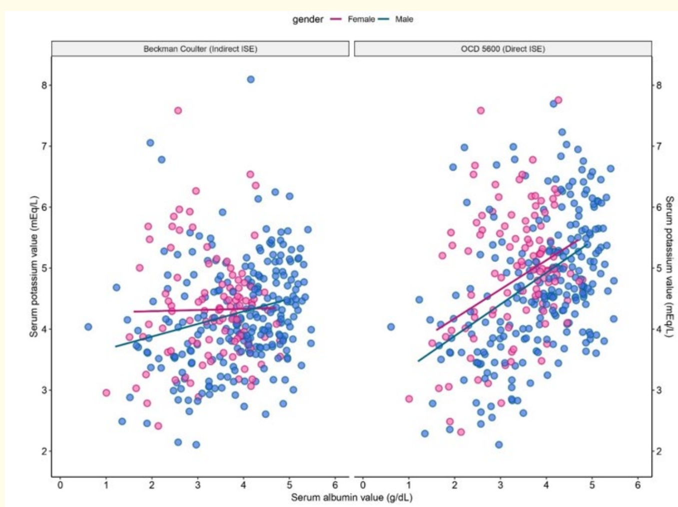

Figure 6: *Association between serum K+ and serum albumin.*

The scatter plots demonstrate the association of serum K^+ and serum albumin values of the female and male participants. The subgroup analysis was performed based on the methods of assessment. The regression lines imply the association of these values among female and male participants.

Discussion

In this retrospective study, we evaluated and compared serum Na^+ and K^+ values of the female and male participants measured through dISE and iISE methods. Additionally, we analyzed the correlation of these parameters with serum total protein and albumin.

We found that mostly elderly individuals had deranged levels of serum Na^+ and K^+. Males were more affected than female participants. Regardless of gender, the electrolyte measurements by the indirect method had more dispersion as compared to the direct method. A majority of participants had different serum electrolyte values when gauged through different methods. The study conducted by Veronique Stove., *et al*. showed that many hospitalized patients had falsely elevated serum Na^+ and K^+ values with decrease in protein concentrations [7]. Lately, some studies [13-15] demonstrated that serum sodium values drop drastically in the individuals with hypoalbuminemia.

The serum electrolyte levels might alter or even show false high or low levels among the persons with chronic liver disease, hypoproteinemia, prolonged hospitalization, on total parenteral nutrition [11,16,17]. We found positive correlations among the serum electrolyte and protein levels. However, these associations were not statistically significant.

To the best of our knowledge, this is the first study to juxtapose two different methods of electrolyte estimation (i.e., dISE and iISE). Our study has a few limitations as well. First, the sample size was relatively small. Second, we did not perform any subgroup analysis based on the duration of hospitalization, the medication history, and comorbidities.

Conclusion

We encountered that the direct (dISE) and indirect (iISE) approaches for estimating serum Na^+ and K^+ levels are comparable. The correlation plots proved that the direct (dISE) technique is substantially better than the indirect (iISE) method. Nevertheless, the correlations were not of statistical significance.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Funding Source

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