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RESEARCH ARTICLE

Perturbations of serum electrolyte levels in iron deficiency anemia - A comparative analysis

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ABSTRACT

Background: Iron deficiency anemia (IDA) and electrolyte imbalance are widely prevalent problems in Indian population. Although few studies have linked IDA with altered serum electrolyte levels, their results were inconsistent. Since IDA is a major public health problem, the suggested relationship between the two assumes clinical importance. In IDA, red cell membrane-bound Na^+K^+ATase activity is altered affecting the serum electrolyte levels. **Aims and Objectives:** To evaluate the alterations in serum electrolyte levels in patients with IDA and comparing it with subjects without anemia. **Materials and Methods:** Totally, 300 subjects (163 with IDA and 137 without anemia) were included. Blood samples analyzed for serum electrolytes, complete hemogram, and iron profile. **Results:** We observed significantly lower serum levels of sodium, higher potassium, as well as chloride in IDA patients when compared with subjects without anemia ($P = 0.0001^{**}$). In IDA patients, a significant positive correlation existed between serum sodium levels with all red cell indices except mean corpuscular volume (MCV) and between bicarbonate levels with hemoglobin (Hb), red blood cell (RBC) count, hematocrit (HCT), and MCV. We observed significant negative correlation between serum potassium levels with Hb, RBC count, HCT, and Mean Corpuscular Hemoglobin Concentration (MCHC) and between chloride levels with Hb and HCT. We found a highly significant association in serum sodium and potassium levels as severity of anemia worsen when compared with chloride and bicarbonate levels. **Conclusion:** Differences in serum electrolyte levels exist between patients with IDA and without anemia. Hence, IDA patients should be monitored closely for their electrolyte levels to avoid complications and better management.

KEY WORDS: Electrolytes; Anemia; Iron Deficiency Anemia; Na^+K^+ATase

INTRODUCTION

Anemia is the most common blood disorder, affecting about a third of the global population. Anemia is responsible for about 800,000 deaths per year worldwide. Nutritional anemia is of more concern in the developing countries having high prevalence rate due to dietary iron deficiency (ID).[1] Approximately one-third of patients with anemia exhibit ID.[2] The annual incidence rate of ID anemia (IDA) is 7.2–13.96 per 1000 people per year.[3]

Iron is vital for human health and defects in iron homeostasis result in serious pathologic abnormalities such as hemochromatosis and anemia.[4] ID is the world's most widespread nutritional disorder, irrespective of age, gender,

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and socioeconomic status, affecting both industrialized and developing countries. In ID , there is insufficient iron to maintain normal physiologic functions.[5] IDA, the most common type of anemia, is an important public health problem because of its complications.[6]

Electrolytes such as sodium (Na^{+}), potassium (K^{+}), chloride (Cl^{-}), and bicarbonate ($HCO3^{-}$) Comprise about 1% of plasma in blood. They are essential for intermediary metabolism and play an important role in controlling fluid levels, nerve conduction, acid-base balance, blood clotting, and muscle contraction. The balance of electrolytes in the body is necessary for the normal functioning of cells and organs and also for the maintenance of red blood cell (RBC) shape, O2/CO2 exchange between red cells and tissues.[7] The calcium-sensitive K^{+} channels regulate the process of erythrocyte apoptosis.[8]

The red cell membrane-bound $Na^{+}K^{+}$ATPase play a principal role in the regulation of intra- and extra-cellular cationic homeostasis.[9] Regulation of these ions is primarily achieved by the Na+/K+ pump, fuelled by ATP energy of metabolism. ATPase, found in RBC membranes, activates the stored ATP energy to change the conformation of membrane proteins which exchange three Na^{+} ions for two incoming K+ ions - an exchange which opposes the ions' electrochemical gradients. This example illustrates the necessity of energy use in actively transporting key cations between the body compartments to maintain vital functions of the circulatory system.[7]

Previous studies have stated that there is an elevation of $Na^{+}K^{+}$ATPase activity in the primary anemia patients. This elevation may compensate the mechanism for adaptation of the patients with low oxygen and its physiological role in the cell.[10]

In IDA, the activity of red cell membrane-bound $Na^{+}K^{+}$ATPase is altered, affecting level of serum sodium and potassium levels.[3,11,12] Furthermore, few studies have reported changes in serum electrolyte levels in sickle cell anemia and[11,13-18] β-thalassemia major.[11,19]

Our interest in the distribution of serum electrolytes in IDA was stimulated by the observation of contradicting reports and also due to paucity of studies done relating the alterations of serum electrolyte levels in anemia. Hence, we aimed to evaluate the alterations in serum electrolyte levels in patients with IDA and comparing it with healthy subjects without anemia.

MATERIALS AND METHODS

This was a descriptive analytical cross-sectional study carried over a period from July 2016 to July 2017 in SRM Medical College Hospital and Research Centre, Institutional Ethical Clearance obtained. Totally, 300 subjects aged more than 20 years of both genders (163 with IDA and 137 without anemia) were included in this study. Their blood samples were analyzed for hemoglobin (Hb), RBC, hematocrit (HCT), mean corpuscular volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), peripheral smear, serum iron, and ferritin levels. Medical history was recorded.

The anemic patients were selected based on their Hb levels (Hb <13 g% in males and <12 g% in females) based on definition of the World Health Organization.[8] Moreover, those with predominantly microcytic red cell indices (MCV <76 fl), hypochromic red cell indices (MCH <27 pg/cell and MCHC <32 g/dl), and on their peripheral smear (microcytic hypochromic) were considered to have IDA which was confirmed by low serum iron (<59 μg/dl in males and <37 μg/dl in females) and low serum ferritin (<15 ng/ml in males and <9 ng/ml in females). Patients suffering from kidney diseases, thyroid disorders, infectious disease, chronic systemic inflammatory disorders, and pregnant woman were excluded from the study.

Hb, RBC, HCT, MCV, MCH, and MCHC were estimated by SYSMEX XT-1800i analyzer. Serum ferritin (Bio-Rad Quanimune Ferritin IRMA, Bio-Rad lab) and serum iron (TPTZ method). Serum analysis for electrolytes was performed by ISE – direct method using Medica EasyLyte automatic analyzer.

Statistical Analysis

The data are presented as mean ± standard error of the mean for continuous variables. A Student's *t*-test was applied for comparison of group means. Pearson's coefficient was calculated to determine correlation between two variables. $P < 0.05$ was considered statistically significant.

RESULTS

Our study results show a statistically significant difference ($P = 0.0001^{**}$) in mean Hb levels in patients with IDA and without anemia (10.5 ± 0.13 g/dl and 14.2 ± 0.12 g/dl, respectively). The mean RBC count, HCT, MCV, MCH, MCHC in patients with IDA, and without anemia were 3.5 ± 0.04, 31.2 ± 0.43, 72 ± 0.9, 24 ± 0.20, 29.6 ± 0.25 and 4.9 ± 0.04, 40.4 ± 0.34, 81.2 ± 0.75, 28.6 ± 0.18, and 34.1 ± 0.16, and the difference was statistically significant ($P = 0.0001^{**}$). The mean serum iron and ferritin levels in patients with IDA and without anemia were 32.68 ± 0.71, 10.06 ± 0.79 and 75.26 ± 0.79, and 45.19 ± 1.11 ($P = 0.0001^{**}$). These data are presented in Table 1.

In this study, we observed that serum sodium levels were significantly lower ($P = 0.0001^{**}$) and serum potassium

(P = 0.0001**) as well as chloride levels (P < 0.05) were significantly higher in patients with IDA when compared with individuals without anemia. However, there was no significant difference in serum bicarbonate levels between patients with IDA and without anemia [Table 2].

In patients with IDA, we observed a significant positive correlation between serum sodium levels with all red cell indices except MCV and also between serum bicarbonate levels with Hb, RBC count, HCT, and MCV. We also observed a significant negative correlation between serum potassium levels with Hb, RBC count, HCT, and MCHC and also between serum chloride levels with Hb and HCT.

In individuals without anemia, we observed a significant positive correlation between serum sodium levels with MCV, but there was no significant correlation with Hb, RBC count, HCT, and MCV, and we found a significant negative correlation between serum bicarbonate levels with RBC count. There was no significant correlation between other electrolytes with red cell indices [Table 3].

We analyzed and compared serum electrolyte levels with various degree of anemia and found it was highly significant between serum sodium and potassium levels as the severity of anemia worsens when compared with chloride and bicarbonate levels [Table 4].

Table 1: Comparison of red cell indices between anemic IDA and not anemic individuals

RBC indices	Mean±SEM		*t*	*P*
	Anemic (IDA) *n*=163	Not anemic *n*=137		
HB	10.5±0.13	14.2±0.12	19.8	0.0001**
RBC count	3.5±0.04	4.9±0.04	21.7	0.0001**
HCT	31.2±0.43	40.4±0.34	16.2	0.0001**
MCV	72±0.9	81.2±0.75	7.7	0.0001**
MCH	24±0.20	28.6±0.18	16.3	0.0001**
MCHC	29.6±0.25	34.1±0.16	14.4	0.0001**

*Significant (P<0.05), **Highly significant (P=0.0001). IDA: Iron deficiency anemia, RBC: Red blood cell, HB: Hemoglobin, HCT: Hematocrit, MCV: mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, SEM: Standard error of the mean

Table 2: Comparison of electrolyte levels between anemic (IDA) and not anemic individuals

Electrolyte	Mean±SEM		*t*	*P*
	Anemic (IDA) *n*=163	Non Anemic *n*=137		
Sodium	130.04±0.55	134.05±0.37	−6.038	0.0001**
Potassium	4.55±0.06	4.17±0.05	5.167	0.0001**
Chloride	104.31±0.50	102.59±0.46	2.522	0.012*
Bicarbonate	23.45±0.36	23.61±0.35	−0.329	0.743

*Significant.(P<0.05), **Highly significant (P=0.0001). IDA: Iron deficiency anemia

In this study, we observed that majority 50.4% of cases without anemia had normal serum sodium levels. Most of the patients with mild anemia had normal (53.7%) and mild hyponatremia (31.5%) and those with severe anemia had severe hyponatremia. Hence, there was a statistically significant association between severity of anemia and hyponatremia (P = 0.0001**) [Table 5].

DISCUSSION

IDA and electrolyte imbalance are widely prevalent problems in the Indian population. Although few studies, both in animals[20] and in humans[11] have linked IDA with altered serum electrolyte levels, the relationship between them has long been a topic of debate in the literature. Since IDA is recognized as major public health problem, the suggested relationship between the two assumes clinical importance. Moreover, the number of published studies investigating electrolyte alterations in IDA is relatively low, and the available data of the results of these studies are inconsistent. Some of these studies show that electrolyte parameters in iron-deficient patients are higher in value than those of healthy control patients, whereas others indicate lower levels in ID.[13,18,19]

In our study, we evaluated the alterations in serum electrolyte levels in 163 patients with IDA and compared it with 137 healthy subjects without anemia. Our study has several important findings. In our study, the serum sodium levels were significantly lower in patients with IDA when compared to individuals without anemia, and also we found a significant positive correlation between serum sodium levels with all red cell indices except MCV and a statistically significant association between severity of anemia and hyponatremia which is in accordance with results of Shraf *et al*.[3] and Agoreyo and Nwanzen.[14] We observed that serum potassium levels were significantly high in IDA patients when compared to individuals without anemia and a significant negative correlation between serum potassium levels with Hb, RBC count, HCT, and MCHC which coincides with results of Agoreyo and Nwanzen[14] but contrasts with study results of Shraf *et al.*[3] who observed lower serum levels of potassium in patients with IDA. We observed a significantly higher level of serum chloride in IDA patients when compared with subjects without anemia and a significant negative correlation between serum chloride level with Hb and HCT.

Previous studies have stated that normal red cells have high level of intracellular potassium and low level of sodium within the extracellular environment. On the other hand, the level of potassium is low in the extracellular environment while that of sodium is high. Na^+ and K^+ ions are restricted to their compartment but can penetrate the cellular membrane

Table 3: Correlation between serum electrolytes and red cell indices levels among anemic (IDA) and not anemic individuals

Study group	Electrolyte	Hb		RBC		HCT		MCV		MCH		MCHC	
		r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Anemia (IDA)	Sodium	0.427	0.0001**	0.165	0.036*	0.406	0.0001**	0.162	0.058	0.173	0.027*	0.196	0.012*
	Potassium	−0.412	0.0001**	−0.212	0.007*	−0.374	0.0001**	−0.043	0.622	0.019	0.814	−0.177	0.024*
	Chloride	−0.222	0.004*	−0.037	0.641	−0.210	0.007*	0.078	0.365	0.144	0.066	−0.014	0.859
	Bicarbonate	0.232	0.003*	0.217	0.006*	0.262	0.001*	0.281	0.001*	0.026	0.739	0.035	0.660
Not anemia	Sodium	−0.042	0.630	−0.135	0.116	−0.058	0.503	0.292	0.0001**	0.110	0.200	0.002	0.981
	Potassium	0.036	0.674	0.127	0.142	0.051	0.554	−0.136	0.083	−0.060	0.484	0.012	0.892
	Chloride	−0.146	0.088	−0.017	0.847	−0.055	0.526	−0.083	0.295	−0.077	0.371	0.130	0.130
	Bicarbonate	−0.118	0.170	−0.179	0.037*	−0.075	0.385	−0.046	0.564	0.125	0.146	−0.050	0.559

*Significant.($P<0.05$), **Highly significant ($P=0.0001$). IDA: Iron deficiency anemia, RBC: Red blood cell, HB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration

Table 4: Comparison of serum electrolyte levels with grades of anemia

Anemia grade	*n*	Mean±SEM			
		Sodium	Potassium	Chloride	Bicarbonate
Mild	54	134.76±4.33	4.06±0.56	102.72±6.36	23.91±3.70
Moderate	87	128.28±6.86	4.74±0.70	104.74±6.17	24.02±4.45
Severe	22	125.41±6.87	4.97±0.66	106.50±6.95	20.05±5.58
t		25.788	23.850	3.201	7.650
P		0.0001**	0.0001**	0.043	0.001*

*Significant.($P<0.05$), **Highly significant ($P=0.0001$), SEM: Standard error of the mean

Table 5: Relationship between serum sodium levels and grades of anemia

Anemia grade	Serum sodium levels *n* (%)			
	Normal	Mild hyponatremia	Moderate hyponatremia	Severe hyponatremia
Normal (*n*=137)	69 (50.4)	49 (35.8)	14 (10.2)	5 (3.6)
Mild anemia (*n*=54)	29 (53.7)	17 (31.5)	7 (13.0)	1 (1.9)
Moderate anemia (*n*=87)	21 (24.1)	9 (10.3)	20 (23.0)	37 (42.5)
Severe anemia (*n*=22)	4 (18.2)	2 (9.1)	3 (13.6)	13 (59.1)

Chi-square: 106.958, ***P*: 0.0001, *Significant

through Na^+K^+ATPase pumps. The red cell Na^+K^+ATPase is a ubiquitous enzyme and plays a central role in the regulation of intra- and extra-cellular cationic homeostasis.[18] Several studies have shown variation in the erythrocyte membrane Na^+K^+ATPase activity was modulated by the changes in the differences resulting from hematological disorders.[11] Furthermore, an increase in red cell membrane permeability to sodium or potassium has been described in a variety of red cell disorders. Previous studies have stated that Na^+K^+ATPase activity is higher in the primary anemia patients. This elevation may compensate the mechanism for adaptation of the patients with low oxygen and its physiological role in the cell.[10]

Several researchers reported that in IDA, the activity of red cell membrane-bound Na^+K^+ATPase is altered and due to this altered ATPase activity, serum sodium, and potassium levels are affected.[3,11,12] Salsbury *et al*. stated that our dietary iron absorption has been mediated by potassium voltage-gated channel subfamily E, member 2 (KCNE 2) which is single-pass integral membrane β subunit of a potassium ion channel. The disruption of this regulatory subunit may also alter the levels of potassium in IDA.[4] This implies that IDA and serum potassium levels are interrelated with each other.

Studies have revealed that electrolyte level alterations also occur in other types of anemia like sickle cell anemia and β-thalassemia. The suggested mechanisms were as follows. Rhoda *et al*. proposed that in sickle cells, an abnormal activation of potassium chloride ($K^+ Cl^-$) cotransport system was involved in cell potassium (K^+) loss and dehydration. Furthermore, he mentioned that potassium chloride ($K^+ Cl^-$) cotransport is abnormally active in erythrocytes containing positive charged Hb such as Hb (S) (HbS).[21] Deoxygenation is known to increase cation permeability of sodium (Na^+), Potassium (K^+), and calcium (Ca^{2+}) in sickle cells.[22] Luthra and Sears proposed that in β-thalassemia patients, oxidative damage induced by free globin chains has been implicated in the pathogenesis of the membrane abnormalities. He also mentioned that Na^+, K^+ pump was reduced in thalassemia-like cells, whereas it was increased in severe alpha- and beta-thalassemia cells. Thus, oxidative damage causes increased activity of K^+, Cl^- cotransport, and hence, K^+ loss in beta-thalassemia erythrocytes.[23] Karim *et al*. suggested that an increased sodium level in β-thalassemia patients may be due to renal damage resulting from iron overload.[19]

Strengths and Limitations

Although studies have reported alterations in serum electrolyte levels in anemia, the results of our study indicated that there was a direct correlation between electrolytes and IDA, hence revealing and adding further evidence to the fact that iron plays a pathogenic role contributing to the maintenance of electrolyte balance in our body. Few limitations of this study were small sample size and with this cross-sectional design, we could not evaluate the mechanism by which IDA affects serum electrolytes and also, we could not follow-up the electrolyte levels after iron therapy. Hence, further multicentric research with larger same size is warranted for accurate assessment of the association of anemia and electrolyte imbalance.

In summary, findings of the present study revealed a significant difference in serum electrolytes, especially sodium, potassium, and chloride levels between patients with IDA and without anemia.

CONCLUSION

Serum electrolyte levels are altered in patients with IDA. Based on our results, we suggest that IDA patients should be monitored closely for their electrolyte levels to avoid complications and better management. The impact of this study might have been improved by studying the electrolyte levels following iron replacement therapy.

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