ORIGINAL ARTICLE

Evaluation of Serum Electrolytes in Sickle Cell Disease Patients with Respect to Hydroxyurea Therapy

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Abstract

Background: Sickle cell disease is one of the oldest genetic disorders known to medical science. The morbidity and mortality associated with the disease and its complication, sickle cell crisis, amounts to be a significant health issue. Hydroxyurea, originally used as an anticancer agent, has proved to be the wonder drug in lower doeses in sickle cell diease. The severity and impact of the disease on the affected person is decreased by a great extent by its use. The mechanism of action of the drug in sickle cell disease is yet to be completely understood. Electrolytes play a crucial role in the pathophysiology of sickle cell disease.

Aim: The current study aims to evaluate the serum electrolyte levels in sickle cell disease patients and look for the effect of hydroxyurea on them.

Materials and methods: Fifty two sickle cell disease (SS) patients and 20 normal individuals were included in the study (AA). Thirty four of the SS patients were under hydroxyurea therapy. The serum levels of magnesium, sodium, potassium, chloride, calcium, phosphate were estimated in all the study subjects.

Results and discussion: No significant difference was found with respect to the serum electrolytes in the sickle cell patients under and not under hydroxyurea therapy. But the serum electrolytes varied significantly between the sickle cell disease patients and the normal individuals.

Conclusion: Serum electrolytes play a crucial role in the pathophysiology of sickle cell disease, but hydroxyuera therapy does not seem to play a great role in altering their levels in the patients.

Keywords: Electrolytes, Hydroxyurea, Sickle cell anemia, Serum magnesium.

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Introduction

Sickle disease affects millions of people worldwide. But in India, its prevalence is higher in central of Madhya Pradesh, Orissa, and Chhattisgarh and western regions of Gujarat and Maharashtra. Sickle cell disease is an autosomal blood disorder that is caused by a point mutation at codon 6 of the *HBB* gene at chromosome,[11] which replaces negatively charged hydrophilic glutamic acid with the nonpolar hydrophobic valine.[1] During deoxygenation, hydrophobic interactions are formed between valine of HbS molecule to the phenylalanine (Phe–85) and leucine (Leu-88) of adjacent Hb molecule.[2] This induces polymerization of sickle hemoglobin molecules to the group, forming long bundles which leads to a marked increase in intracellular viscosity and elastic stiffness that indirectly affects the cell membrane forming rod-like structures, distorting the structure from normal disc to sickle shape.[1]

Some clinical observations have suggested that increased fetal hemoglobin concentrations may have beneficial effects in sickle cell anemia. Fetal hemoglobin which lacks β-globin chain inhibits sickling in vitro by interfering with the polymerization of hemoglobin S.[3] Hydroxyurea is an inhibitor of ribonucleotide reductase, increasing fetal hemoglobin in red blood cells and decreasing the frequency of pain events. Promoting the appropriate use of hydroxyurea is a promising way to improve health outcomes among patients with sickle cell disease.[4] It has no role in the treatment of pain crises in progress, neither is it approved by the Food and Drug Administration but many of the clinical data supports its use for the prevention of pain crises.[5]

Electrolytes are substances that become ions in solution and acquire the ability to conduct electricity. Many of the studies involving sickle cell patients have shown that there are increased and continued obligatory losses of body fluids and electrolytes resulting in dehydration and other metabolic disturbances. Thus a proper balance of electrolytes in the body is essential for the normal functioning of cells and organs.[5] Electrolytes have normal range values, and complications may arise if any electrolytes are higher or lower than the normal range values.[6]

The rate and extent of polymer formation in red blood cells are profoundly influenced by the intracellular concentration of hemoglobin S in which the hydration state of these cells plays a critical factor. Dehydration of sickle erythrocytes which follows the loss of solute and osmotically obliged water resulting from increased efflux of potassium by two specific pathways: the potassium-chloride cotransport pathway and the calcium-activated potassium efflux (or Gardos) pathway.7 The Gardos pathway activates by an increase in cytosolic-free calcium, which induces Ca2+ entry into the cell mediating potassium and water loss. The K–Cl cotransport is activated everytime sickle cells are exposed to pH below 7.40 leading to loss of K+, Cl– and water.8

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This study was carried out to determine the serum electrolyte levels into two groups of patients who are going through hydroxyurea therapy and without hydroxyurea therapy in sickle patients with comparing their values from another group of control. We have focused on specific serum electrolytes concentrations of sodium, potassium, chloride, calcium, magnesium, and phosphate. This study may show the way for pathophysiology-directed therapy, possibly highlighting some of the avoided aspects associated with electrolyte imbalances.

Materials and methods

The study was done in the Department of Biochemistry, Pt. JNM Medical College, Raipur, in collaboration with Sickle Cell Institute Chhattisgarh, Raipur. The study includes three groups: two groups of sickle patients both going through hydroxyurea therapy and patients without any history of hydroxyurea therapy. The subjects were chosen randomly, in which 52 individuals with sickle cell disease were taken which later were distinguished into 34 patients having hydroxyurea while 18 patients were taken without any hydroxyurea therapy and 20 healthy individuals were taken as control. Detailed information was elicited by written consent from the patients.

Inclusion Criteria

Samples were collected from the patients attending the sickle cell OPD in SCIC, Raipur, who had been diagnosed with sickle cell disease.

Exclusion Criteria

Patients who had gone through blood transfusion in the last 60 days and those suffering from any other hemoglobinopathy.

Sample Collection

Three mL of blood was collected through venipuncture and kept for half an hour to clot, at room temperature. Serum was separated through centrifugation at 3000 rpm for three minutes and was transferred to plain vacutainer for serum electrolyte estimation.

Biochemical Analysis

The concentration of serum sodium, potassium and chloride were done in electrolyte analyzer whereas calcium was done in autoanalyzer. Magnesium and phosphate concentrations were determined by accucare magnesium xylidyl blue (MAG 25) and accucare phosphorus UV end-point method (PHOS 100 PHOSM 25) kits respectively. With this, certain routine parameters were taken for checking the hepatic and renal function of sickle patients.

Statistical Analysis

The values were expressed as mean± standard deviation and student t-test was used to calculate the significant differences at $p < 0.05$.

Result

Fifty-two individuals with sickle cell disease (within 0-55 years) of age and 20 healthy individuals as control (within 18 to 50 years of age) were included in the study.

The serum levels of most of the electrolytes(Na, K, Cl, PO_4) was significantly higher in the sickle cell disease patients with respect to the normal individuals. But no significant difference was found in the Ca and Mg levels. There was also a significant difference in the routine parameters like renal function tests and liver function tests between the two groups (Table 1). Among the sickle cell disease patients, those who were under hydroxyurea therapy didn't have any significant difference from those not taking hydroxyurea ($p > 0.05$) only expect AST ($p = 0.016$) (Table 2).

Discussion

In our study, the serum sodium and potassium levels were found to be significantly higher in the sickle cell disease patients. This was in concordance with some previous findings.[9] Agoreyo etal. too found a higher level of serum potassium in sickle cell disease.[6,10] Clark et al. suggested that dehydration and deoxygenation caused excessive potassium losses, resulting in cation depletion. This later gets accumulated in the extracellular environment giving abnormally elevated values in sickle patients.[11]

From results of the present study, calcium and chloride levels were found significantly higher in the serum of sickle cell patients as compared to control. The previous finding supported this in which increased levels of calcium in sickle patients were found when compared to control.[7]

The magnesium levels were found to be lower in the sickle cell patients than the controls but the difference was not significant ($p = 0.2$).

Table 1: Comparative study of biological parameters between sickle cell patients and control

Characteristics	*Sickle cell patients* (n = *52)*	*Control* (n = *20)*	*p value*
Age	15.4 ± 12.02	23.9 ± 6.35	0.004
Sex (M:F)	24:28	9:11	0.018
Total bilirubin (mg/dL)	2.85 ± 2.7	0.80 ± 0.58	0.001
Direct bilirubin (mg/dL)	0.7 ± 1.8	0.23 ± 0.12	0.2
AST (IU/L)	23.7 ± 25.5	15.4 ± 5.9	0.1
ALT (IU/L)	33.2 ± 26.1	20.2 ± 10.3	0.03
Urea (mg/dL)	14.7 ± 5.7	26.9 ± 6.4	<0.0001
Creatinine (mg/dL)	0.15 ± 0.16	0.7 ± 0.1	<0.0001
Sodium (mmol/L)	135.2 ± 4.02	131.2 ± 4.4	0.0005
Potassium (mmol/L)	4.23 ± 0.86	3.8 ± 0.3	0.03
Chloride (mmol/L)	105.1 ± 4.28	98.6 ± 3.9	<0.0001
Calcium (mg/dL)	9.35 ± 0.69	8.8 ± 0.9	0.02
Magnesium (mg/dL)	2.10 ± 0.36	2.2 ± 0.14	0.2
Phosphate (mg/dL)	4.31 ± 0.37	3.95 ± 0.46	0.001

Table 2: Comparative study of biological parameters between hydroxyurea and non-hydroxyurea patients

Characteristics	*Sickle cell patients* (n = *52)*	*Control* (n = *20)*	*p value*
Age	18.8 ± 16.2	13.7 ± 8.51	0.1
Sex (M:F)	9:9	15:19	0.05
Total bilirubin (mg/dL)	2.9 ± 1.4	2.3 ± 1.3	0.1
Direct bilirubin (mg/dL)	1.15 ± 0.32	1.47 ± 0.8	0.1
AST (IU/L)	35.3 ± 19.7	17.6 ± 7.1	< 0.01
ALT (IU/L)	34 ± 17.6	28.1 ± 11.6	0.15
Urea (mg/dL)	16.6 ± 6.7	13.7 ± 4.8	0.09
Creatinine (mg/dL)	0.51 ± 0.17	0.52 ± 0.15	0.7
Sodium (mmol/L)	133.9 ± 3.4	135.9 ± 4.1	0.08
Potassium (mmol/L)	4.4 ± 1.3	4.1 ± 0.4	0.13
Chloride (mmol/L)	105 ± 2.8	104.8 ± 4.8	0.4
Calcium (mg/dL)	9.31 ± 0.5	9.38 ± 0.7	0.7
Magnesium (mg/dL)	2.05 ± 0.2	2.13 ± 0.4	0.4
Phosphate (mg/dL)	4.35 ± 0.35	4.30 ± 0.39	0.6

Some findings supported the study, in which magnesium levels were found in decreased concentration in sickle cell patients.[13] Digban also reported that the levels of magnesium were found in decreased values in sickle cell patients.[14]

From the study, phosphate levels were found significantly higher in sickle cell patients compared to control ($p < 0.05$). Oladipo also reported increased levels in sickle patients than in control.[15]

Conclusion

Electrolytes play an important role in the pathophysiology of sickle cell disease and their abnormalities can cause severe complications. Dehydration due to these abnormalities induces sickling. From this study, it was found that the serum levels of most of the electrolytes vary significantly between sickle cell disease patients and controls but between the two groups, of sickle cell patients with hydroxyurea and without hydroxyurea here was no statistically significant.

The study had two limitations. The sample size of the study was relatively small. Follow up studies of repeated measurements of serum electrolytes can give better insights into understanding the importance of electrolytes in the pathophysiology of sickle cell disease.

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