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ELEVATED MEAN CELL VOLUME IN SICKLE CELL ANAEMIA: ONE STORY, TOO MANY?

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Abstract: **Introduction:** Sickle cell disease is a hereditary blood disorder characterized by defective hemoglobin. Red cell indices are proposed as potential tools for diagnosing and managing sickle cell disorders.

Materials and Methods: This study aimed to assess the utility of red cell indices as screening tools for sickle cell anemia. One hundred consenting adults of both sexes participated. Haematological parameters, including packed cell volume, hemoglobin values, hemoglobin electrphoretic patterns, and red blood cell count, were examined. Mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), and mean cell hemoglobin (MCH) were calculated. Data analysis was performed using GraphPad Prism Software Version 9, with statistical significance set at $p < 0.05$ (95% confidence interval).

Results: Haemoglobin values were significantly lower in Hb SS subjects (5.68 ± 1.7g/dl) compared to Hb AA (11.30 ± 1.5 g/dl) and Hb AS groups (11.03 ± 1.4 g/dl) ($F = 32.279$; $p < 0.00001$). The pattern was consistent with PCV and RBC values. Among the red blood cell indices assessed, only MCV showed a significant elevation (95.7 ± 2.4 fl) in the HbSS group compared to other groups ($F = 4.165$; $p = 0.0183$). No statistically significant difference was observed in MCHC and MCH values between the three groups ($F = 0.5373$, $p > 0.586$ for MCHC; $F = 0.607$, $p > 0.546$ for MCH). The prevalence of haemoglobin variants was as follows: HbAA (77%), HbAS (19%), and HbSS (4%).

Conclusion: This study highlights significant reductions in haemoglobin values in Hb SS subjects and a notable elevation in MCV values in the Hb SS blood group. Elevated MCV in sickle cell anemia, where red cells are typically microcytic, warrants further investigation for differential diagnosis.

Keywords: Mean Cell Volume, Sickle Cell Anemia, Haemoglobinopathies, Port Harcourt, Nigeria.

INTRODUCTION

Haemoglobinopathies are the most common genetically inherited disorders. According to the World Health Organization (WHO), approximately 5% of the world's population carries genetic haemoglobin (Hb) disorders. Each year, over 42 million individuals are carriers, and more than 12,000 infants are born with major and clinically significant haemoglobinopathies. The worldwide migration of human populations and the relatively higher frequency of consanguineous marriages in many countries have contributed to the increased burden of haemoglobinopathies (1-4).

These disorders primarily affect populations in malaria-endemic regions and those with a history of consanguineous marriages, posing a significant public health burden. The clinical spectrum of haemoglobinopathies varies widely, ranging from asymptomatic carriers to severe anaemias and life-threatening complications such as acute chest syndrome and organ damage (3).

Early diagnosis and accurate classification of haemoglobinopathies are crucial for appropriate clinical management and genetic counseling. Traditionally, laboratory tests including haemoglobin electrophoresis and DNA analysis have been the gold standard for definitive diagnosis. However, these methods are often costly, time-consuming, and require specialized equipment and expertise, thereby limiting their utility in resource-limited settings (5, 6). There is, therefore, a growing interest in exploring alternative screening tools that are cost-effective, easily accessible, and capable of providing rapid results.

Red cell indices, including mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC), have been proposed as potential screening parameters for haemoglo-

binopathies. Mean Corpuscular Volume (MCV) measures the average volume or size of a red blood cell, calculated by dividing the total volume of packed red blood cells by the total number of red blood cells in the sample, and is expressed in femtolitres (fl) (7, 8). Mean Cell Hemoglobin (MCH) represents the average amount of hemoglobin in a single red blood cell, calculated by dividing the total amount of hemoglobin by the total number of red blood cells in the sample, and is measured in picograms (pg) (8). Mean Cell Hemoglobin Concentration (MCHC) measures the concentration of hemoglobin in a given volume of packed red blood cells, calculated by dividing the total amount of hemoglobin by the total volume of packed red blood cells, and is expressed in grams per litre (g/L) (8).

These indices are routinely measured as part of full blood counts (FBC) in clinical practice, making them readily available and integrated into standard laboratory procedures (9). The rationale behind their potential usefulness lies in the fact that different types of haemoglobinopathies manifest with distinct erythrocyte morphologies and hemoglobin content, leading to alterations in the red cell indices.

Anaemia is characterized by a reduction in hemoglobin (Hb) or hematocrit (HCT) or red blood cell count (RBC) and can be subdivided into macrocytic, microcytic, or normocyticanaemia (10).

Mean Cell Volume (MCV) classifies anaemia into three main categories: microcytic (small cells), normocytic (normal-sized cells), and macrocytic (large cells). These classifications help in identifying potential underlying causes of anaemia. For example, microcyticanaemia is caused by iron deficiency or thalassaemia, while macrocyticanaemia is caused by vitamin B_{12} or folate deficiency (11).

Mean Cell Haemoglobin (MCH) assesses the amount of haemoglobin present in the cells, aiding in the classification of anaemia. Low MCH levels may suggest iron deficiency anaemia, thalassaemia, vitamin B_{12}, or folic acid deficiency, as well as macrocyticnormochromicanaemias (8, 11).

Mean Cell Haemoglobin Concentration (MCHC) provides information about the colour or colour intensity of the red blood cells and is useful in diagnosing certain types of anaemia like hypochromicanaemia, which characterizes iron deficiency (11).

Using these red cell indices, healthcare professionals can diagnose anaemia and differentiate between different types of anaemia. This differentiation is crucial for determining the underlying cause of the anaemia and guiding appropriate treatment strategies (11).

There is a need to systematically assess the usefulness of these red cell indices in detecting and characterizing haemoglobinopathies to determine their reliability and clinical significance.

Aim

This study aims to evaluate the diagnostic potentials of red cell indices as a screening tool for the identification of sickle cell anaemia.

MATERIALS AND METHODS

Study Area

This study was conducted at the Rivers State University Teaching Hospital (RSUTH) (formerly Braithwaite Memorial Specialist Hospital) in Port Harcourt, a government-owned hospital located at 5-8 Harley Street, Old GRA, Port Harcourt, Rivers State, Nigeria. Its GPS coordinates are 4.7843°N 7.0104°E. The hospital, ranked among the largest in the Niger Delta, has a capacity of 375 beds and accreditation in most clinical departments. Port Harcourt, the capital and largest city in Rivers State, Nigeria, has a population of about 1,148,665 (12). It is a major hub of activities and a new frontier of opportunity for various economic, social, and political interests.

Study Population

The study population comprised patients attending the sickle cell clinic at RSUTH who were referred to the haematology laboratory for confirmation of their sickle cell status. One hundred adults of both sexes who consented to participate were included in the study.

Study Design

This study was a cross-sectional observational study designed to assess the usefulness of red cell indices as screening tools for haemoglobinopathies.

Sample Size Calculation

The minimum sample size was determined using the global prevalence of haemoglobinopathies (7%) as reported by Wendt *et al* (13). The formula used for calculation was:

$$n = \frac{Za^2 pq}{d^2}$$

Where n = Minimum sample size

Z = Standard normal deviation corresponding to 95% confidence level set at 1.96

p = 7% = 0.07

q = 1 – p = 0.93

d = desired precision, 5% (0.05)

$$n = \frac{1.96(0.07 \times 0,93)}{(0.05)^2}$$

$$n = 51$$

Ethical Considerations

Ethical approval was obtained from the Office of the Research Ethics Committee, Rivers State University Teaching Hospital. All procedures were performed in accordance with institutional and national research committee ethical standards and with the 1964 Helsinki declaration and its later amendments.

Sample Collection and Storage

Five milliliters (5ml) of blood were aseptically collected from each patient by venipuncture of the cubital vein using sterile disposable vacutainer blood collection needles and bottles. Samples were placed in Ethylenediaminetetraacetic acid (EDTA) bottles and stored at 4-8 °C until analyzed.

Procedures for the Estimation of Complete Blood Count Parameters:

Two (2) ml of blood was placed in another EDTA tube for automated analysis using the hematology auto analyzer Sysmex KX-21N, following the manufacturer's operational guidelines. All samples were analyzed within 30 minutes of collection.

Red Cell Indices Calculations:

The red cell indices were calculated using the standard formulae.

$$MCV = \frac{\text{Hematocrit}(\%)\text{x}10}{\text{RBC}\ (\text{x}10^{12}/\text{L})}$$

$$MCH = \frac{\text{Hb}(\text{g/dL})\text{x}10}{\text{RBC}\,(\text{x}10^{12}/\text{L})}$$

$$MCH = \frac{\text{Hb}(\text{g/dL})\text{x}100}{\text{Hematocrit}(\%)}$$

Determination of Haemoglobin Electrophoretic Pattern by Cellulose Acetate Method

Principle

This method is based on the principle of electrophoresis. Under an electric current, at an alkaline pH (8.4 - 8.6), haemoglobin is a negatively charged molecule and migrates towards the anode (the positively-charged pole of the gel). Haemoglobin variants have alterations in their surface charge due to changes in surface amino acids. This alters the speed of their migration, resulting in characteristic separation based on set mobility patterns.

Procedures

Wash 100µl of EDTA whole blood three times with normal saline using a centrifuge. Carefully decant the supernatant after each wash. Lyse the washed cells with 300 µl of distilled water and allow for 5 minutes. Fill each compartment of the electrophoretic tank with 50ml of Tris-EDTA borate buffer solution at pH 8.6.

Soak the cellulose acetate paper in Tris-EDTA borate buffer for 5 minutes. Remove the impregnated cellulose acetate strip from the buffer with forceps and blot gently between two clean sheets of blotting paper.

Place a wick of filter over each bridge, dipping into the buffer in the tank.

Place a tile on a horizontal surface. Place a drop of the control sample on the tile and a test sample beside it.

Use an applicator to load the control and test samples onto the cellulose acetate paper. Transfer the cellulose acetate paper and place it across the bridge of the tank on the wick of the filter, dipping into the buffer solution.

Close the lid of the tank and switch on the electric power for 10-15 minutes.

Switch off the power, remove the lid, and interpret the result based on the movement of loaded samples from the point of origin.

Statistical analysis

The data generated from this study were analyzed using GraphPad Prism Software Version 9. Statistical significance will be defined as a p-value less than 0.05 at a 95% confidence interval.

RESULTS

This study aimed to assess the usefulness of red cell indices as screening tools for sickle cell anaemia. One hundred subjects participated in the study, with 86% being females and 14% males. The prevalence of haemoglobin variants in the study population was as follows: Haemoglobin AA (HbAA) (77%), Haemoglobin AS (Sickle cell trait) (HbAS) (19%), and Haemoglobin SS (Sickle cell haemoglobin variant) (HbSS) (4%).

Table 1. *Mean ± SD of the haematological indices and association with the haemoglobin electrophoretic patterns*

Haemoglobin Electrophoretic pattern	Sex		Hb (g/dl) Mean ± SD	PCV (%) Mean ± SD	RBC x 10^{12}/dl Mean ± SD	MCHC (g/l) Mean ± SD	MCV (fl) Mean ± SD	MCH (pg) Mean ± SD
	F	M						
HbAA	67	11	11.30 ± 1.5^{a}	34.17 ± 4.2^{a}	3.61 ± 0.4^{a}	33.17 ± 0.3^{a}	94.55 ± 0.7^{a}	3.10 ± 0.02
HbAS	15	2	11.03 ± 1.4^{a}	33.24 ± 4.3^{a}	3.51 ± 0.4^{a}	33.11 ± 0.3^{a}	94.48 ± 0.7^{a}	3.11 ± 0.03
HbSS	4	1	5.68 ± 1.7^{ab}	17.14 ± 5.2^{ab}	1.8 ± 0.4^{ab}	33.04 ± 0.3^{a}	95.7 ± 2.4^{ab}	3.12 ± 0.04
Total	86	14	–	–	–	–	–	–
Mean ± SD			10.981	33.15 ± 5.6	3.505 ± 0.6	33.16 ± 0.4	94.59 ± 0.9	3.10 ± 0.05
F-value			32.27908	36.19111	35.9207	0.53732	4.16529	0.60759
P = value			< .00001***	< .00001.***	< .00001.**	0.586044^{ns}	0.0183*	$0.546724.^{ns}$

Abbreviations: **SD** - Standard deviation; **HbAA** - Haemoglobin AA (Normal haemoglobin); **HbAS** - Haemoglobin AS (Sickle cell trait); **HbSS** - Haemoglobin SS (Sickle cell haemoglobin variant); **Hb** - Haemoglobin; **PCV** - Packed Cell Volume; **MCHC** - Mean Cell Haemoglobin Concentration; **MCV** - Mean Cell Volume; **MCH** - Mean Cell Haemoglobin

Note: Significant differences are denoted as follows: 'a', 'b' for Hb levels, '' for P-values.*

DISCUSSION

This study aimed to evaluate the diagnostic potential of red cell indices as screening tools for haemoglobinopathies. The prevalence of haemoglobin variants observed in this study was Hb AA (77%), Hb AS (19%), and Hb SS (4%). This prevalence rate aligns with the findings of Gboeloh *et al*. (14), where the prevalence of SS subjects was reported as 62.1%, 33%, 4.4%, and 0.5% for HbAA, HbAS, HbSS, and HbAC, respectively. However, the prevalence of sickle cell trait was higher in the study by Gboeloh *et al.* (14). Similarly, Jeremiah (15) reported Hb AA as 80.32% and Hb AS as 19.68%, indicating that the prevalence of haemoglobin variant Hb AS has remained relatively stable over eighteen years.

Another significant finding in this study was a notable reduction in haemoglobin values in the Hb SS blood group. This finding is consistent with the research results of Valavi *et al*. (16), who also observed significantly lower haemoglobin values in individuals with the SS haemoglobin genotype. The pronounced reduction in haemoglobin values observed in individuals with sickle cell anaemia (SCA) is a central haematological hallmark of this inherited blood disorder.

Sickle cell anaemia is characterized by a point mutation in the beta-globin gene, resulting in the substitution of glutamic acid for valine at position 6 of the beta-globin chain of chromosome 11. This genetic alteration leads to the formation of abnormal haemoglobin known as haemoglobin S (HbS), which, under conditions of reduced oxygen tension, triggers the characteristic sickling of red blood cells.

Normal red blood cells typically circulate for approximately 120 days before undergoing natural senescence. In contrast, sickled cells exhibit a significantly shortened lifespan, contributing to a diminished red blood cell count in circulation. This accelerated turnover is a consequence of the increased fragility and vulnerability of sickled cells, rendering them more prone to haemolysis.

Haemolysis, or the premature breakdown of red blood cells, plays a pivotal role in the reduction of haemoglobin values in sickle cell anaemia. The rigid, sickle-shaped cells are more susceptible to rupture as they navigate through the microvasculature, particularly in regions of the body experiencing low oxygen levels. This chronic haemolysis leads to a continuous loss of red blood cells, creating a persistent state of anaemia in affected individuals.

Furthermore, the process of haemolysis in sickle cell anaemia is associated with the release of free haemoglobin into the bloodstream. This free haemoglobin can then undergo oxidation, leading to the formation of methaemoglobin and haemosiderin. The removal and recycling of these byproducts place an additional burden on the body's physiological systems, contributing to the overall depletion of haemoglobin and the downstream consequences of anaemia.

The cyclical nature of haemolysis in sickle cell anaemia results in recurrent drops in haemoglobin levels, often precipitating acute episodes known as haemolytic crises. These crises can be triggered by various factors, including infections, dehydration, or exposure to low oxygen levels. During a haemolytic crisis, there is a rapid and substantial reduction in haemoglobin, exacerbating the symptoms of anaemia and potentially leading to life-threatening complications (17-23).

The study recorded a significant elevation in MCV values in the Hb SS blood group, which is con-

sistent with the study of Akodu et al. (21), where elevated MCV values were reported in Hb SS subjects. The observation of macrocytosis in sickle cell anaemia (SCA) represents a significant haematological phenomenon with multifaceted implications. Macrocytosis, characterized by an elevated Mean Cell Volume (MCV), is attributed to an increase in reticulocytes, which are young, immature red blood cells. This process serves as a crucial adaptive response in the context of SCA, and its underlying mechanisms shed light on the dynamic interplay between haemolysis, haematopoiesis, and the unique pathophysiology of sickle cell disease.

The primary driver of macrocytosis in SCA is the heightened production of reticulocytes, which replace damaged red blood cells in circulation. Reticulocytes, being larger than mature red cells, contribute to the overall elevation in MCV values. This phenomenon is reflected in an MCV greater than 100fl, serving as a distinctive marker of macrocytosis.

The intricate relationship between macrocytosis and ongoing haemolysis in SCA is pivotal to understanding this phenomenon. Haemolysis, the premature breakdown of red blood cells, is a characteristic feature of SCA, primarily driven by the abnormal sickle-shaped morphology of red cells. As these sickled cells navigate through the circulation, they become more susceptible to rupture, leading to a continuous release of haemoglobin into the bloodstream and a subsequent increase in free reticulocytes.

The surge in reticulocyte production can be viewed as a compensatory mechanism initiated by the body in response to the chronic loss of red blood cells through haemolysis. The stimulation of haematopoiesis, the process of blood cell formation, becomes heightened to counteract the ongoing depletion of mature red cells. This heightened haematopoietic activity results in an increased supply of young red cells, characterized by their larger size and elevated MCV values.

The pivotal role of reticulocytes in macrocytosis is further underscored by the fact that young red cells inherently possess higher MCV values compared to their mature counterparts. This physiological characteristic contributes to the overall elevation in MCV observed in individuals with SCA. The increased MCV values in the SS blood group, indicative of macrocytosis, thus emerge as a consequence of the intricate interplay between ongoing haemolysis, heightened haematopoiesis, and the production of young, larger red blood cells.

The insights from Sembulingam et al (19) lend support to the proposed mechanism, emphasizing the dynamic nature of erythropoiesis in response to the unique challenges posed by sickle cell anaemia. The observed macrocytosis in sickle cell anaemia not only serves as a diagnostic indicator but also offers valuable insights into the adaptive responses of the hematopoietic system to the chronic haemolytic stress characteristic of this genetic disorder. Understanding these intricate relationships contributes to a more comprehensive comprehension of the haematological manifestations in sickle cell anaemia and may inform targeted therapeutic interventions aimed at modulating haematopoietic responses in affected individuals.

CONCLUSION

This study concluded as follows: 1) significant reductions in haemoglobin values in the Hb SS subjects. 2) significant elevation in MCV values in the Hb SS blood group. Ideally, MCV is decreased in sickle cell anaemia as the red cells are predominantly microcytes, but when the reverse is the case and MCV becomes elevated, it necessitates further investigations for the purpose of differential diagnosis.

Abbreviations

MCV - Mean Cell Volume
MCHC - Mean Cell Haemoglobin Concentration
MCH - Mean Cell Haemoglobin
ANOVA - Analysis of Variance
GPS - Global Positioning System
RSUTH - Rivers State University Teaching Hospital
WHO - World Health Organization
EDTA - Ethylene Diamine Tetraacetic Acid

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Authors' Contributions: ZJ contributed to conceptualization, detailed review, and statistical analysis. MA contributed to literature review and laboratory analysis. All authors have critically reviewed and approved the final manuscript for submission.

Note: Artificial intelligence was not utilized as a tool in conducting this study.

Sažetak

POVIŠENA SREDNJA ZAPREMINA ERITROCITA U ANEMIJI SRPASTIH ĆELIJA: JEDNA PRIČA, PREVIŠE?

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Uvod: Anemija srpastih ćelija je nasledni poremećaj krvi karakterisan defektnim hemoglobinom. Pokazatelji crvenih krvnih zrnaca se predlažu kao potencijalni alati za dijagnostikovanje i tretiranje poremećaja srpastih ćelija.

Materijali i metodi: Ova studija imala je za cilj procenu korisnosti indeksa crvenih krvnih zrnaca kao alata za pretragu anemije srpastih ćelija. Učestvovalo je 100 odraslih osoba oba pola koje su pristale na učešće. Hematološki parametri, uključujući hematokrit, vrednosti hemoglobina, elektroforetske obrasce hemoglobina i broj crvenih krvnih zrnaca, ispitan je. Izračunate su srednje vrednosti zapremine eritrocita (MCV), srednje koncentracije hemoglobina u eritrocitima (MCHC) i srednje količine hemoglobina u eritrocitima (MCH). Analiza podataka izvršena je korišćenjem softvera GraphPad Prism verzije 9, sa statističkom značajnošću postavljenom na $p < 0,05$ (interval poverenja od 95%).

Rezultati: Vrednosti hemoglobina bile su značajno niže kod osoba sa SS genotipom (5,68 ± 1,7 g/dl) u poređenju sa AA (11,30 ± 1,5 g/dl) i AS grupama (11,03 ± 1,4 g/dl) ($F = 32,279$; $p < 0,00001$). Ovaj obrazac bio je u skladu sa vrednostima hematokrita (PCV) i broja eritrocita (RBC). Među procenjenim indeksima eritrocita, samo MCV je pokazao značajno povećanje (95,7 ± 2,4 fl) u HbSS grupi u poređenju sa drugim grupama ($F = 4,165$; $p = 0,0183$). Nije primećena statistički značajna razlika u vrednostima MCHC i MCH između tri grupe ($F = 0,5373$, $p > 0,586$ za MCHC; $F = 0,607$, $p > 0,546$ za MCH). Učestalost varijanti hemoglobina bila je kako sledi: HbAA (77%), HbAS(19%) i HbSS (4%).

Zaključak: Ova studija ističe značajna smanjenja vrednosti hemoglobina kod osoba sa SS genotipom i primetno povišene vrednosti MCV u krvi osoba sa SS grupom. Povišen MCV u anemiji srpastih ćelija, gde su crvena krvna zrnca tipično mikrocitna, zahteva dalje istraživanje u svrhu diferencijalne dijagnoze.

Ključne reči: Hematokrit, Anemija srpastih ćelija, Hemoglobinopatije, Port Harcourt, Nigerija.

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