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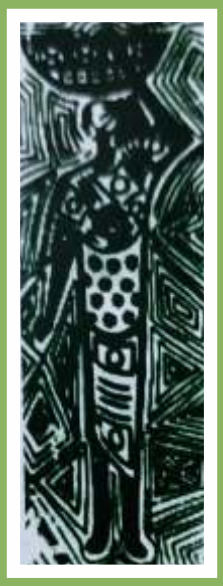

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The Impact of Hydroxyurea Therapy on Clinical and Haematological Parameters in Children with Sickle Cell Anaemia

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Abstract

Background: Sickle cell anaemia (SCA) is an inherited genetic disorder of the erythrocyte that is frequently encountered worldwide. Hydroxyurea is a myelosuppressive and sickle cell disease-modifying agent.

Objective: To determine the effects of six months of treatment with hydroxyurea on the clinical and haematological parameters of children with SCA.

Methods: A longitudinal study involving 58 subjects was used. Clinical and haematological parameters were recorded at recruitment and intervals within six months of the commencement of hydroxyurea. Pre- and post-HU therapy data were compared.

Results: There was a significant reduction in the frequency of vaso-occlusive crises, acute chest syndrome, hospitalisations, stroke and blood transfusions ($p<0.001$ respectively). Haemoglobin F value and packed cell volume increased from a median (IQR) of 6.6% (6.0) to 15.9% (7.6) and from 22.0% (3.9) to 27.0% (3.5), respectively ($p<0.001$ in each case).

Conclusion: This study reports significant improvement in the clinical and haematological profiles of children with SCA following hydroxyurea therapy. Due to its proven clinical and haematological advantages, hydroxyurea should be globally adopted to manage SCA in children.

Keywords: Haematological Profile, Hydroxyurea, Myelosuppressive, Sickle Cell Anaemia, Vaso-occlusive-Crises.

Introduction

Sickle cell disease (SCD) is the commonest inherited haemoglobinopathy worldwide.[1] The combination of the sickle cell gene with any other abnormal β-globin gene gives rise to SCD. Sickle cell anaemia (SCA), a variant of SCD, occurs when both β-globin genes have the sickle cell mutation, resulting in homozygous haemoglobin (Hb) S.[2] At low oxygen tension, the tetrameric HbS molecules precipitate as insoluble polymers, causing deformation of erythrocytes and rendering them relatively inflexible and unable to traverse the capillary beds. Vaso-occlusion, haemolysis, and a wide range of other complications ensue, resulting in significant morbidity and mortality.[2]

SCA-related morbidity and mortality rates are still relatively high, especially in sub-Saharan Africa (SSA), and constitute a significant burden

to the patients, their caregivers and healthcare practitioners.[3,4] SCA is a cause of frequent admissions in any paediatric unit, and this constitutes a significant burden on their caregivers.[5] Abhulimeh-Iyoha *et al*.[6] in Benin City reported that SCA accounted for about 12 per cent of admissions with a case fatality rate of three per cent, which was slightly higher than the case fatality rate reported by Brown *et al*.,[7] in Ibadan. Patients with SCA have a variety of complications which occur throughout their lives and affect virtually all systems of the body, including hepatic and renal involvement. These complications have been attributed to chronic sickling within the systems.[8,9]

Hydroxyurea (HU) is a urea analogue and anti-metabolite which was initially used to treat leukaemias but was first tested in adults with SCD in 1984.[10] It works mainly by inducing the production of foetal haemoglobin (HbF); thus, preventing the formation of HbS polymer.[1] Hydroxyurea has been shown to prevent and reduce SCA-related complications by 40%.[11] Studies in developed countries have reported its efficacy, effectiveness and tolerability in children.[12,13] Yawn and John-Sowah[3] in the United States asserted that HU is still been underused despite its documented clinical and biochemical benefits, and this was also corroborated by Adewoyin *et al*.[14] Reasons for this observed suboptimal use include inadequate awareness of the drug among practitioners, cost, unavailability, fear of unknown effects by both patients and healthcare providers and lack of adequate data on the effectiveness of HU.[11,15]

Haematological abnormalities are critical complications in SCA hence it is expedient to monitor the impact of Hydroxyurea (HU) on haematological parameters such as full blood count (FBC), haemoglobin (Hb) levels, haematocrit (HCT), white blood cell count (WBC), platelet count, and foetal haemoglobin (HbF). These parameters are vital for assessing the therapeutic efficacy of HU, particularly in children. Studies on HU's effect on these clinical and haematological parameters have been mostly done in adults.[3,14,16,17] While some studies have focused on paediatric age groups in Nigeria and Sub-Saharan Africa (SSA),[18-20] it remains crucial to evaluate the promising effects of HU in improving morbidity and mortality in children with SCA. This study aimed to determine the effects of six months of treatment with hydroxyurea on the clinical and haematological parameters of children with SCA.

Methods

Study design

The study was a hospital-based, longitudinal study carried out over nine months.

Study site

The study was conducted at two referral hospitals in Abeokuta, the capital of Ogun state in southwest Nigeria.

Structure of the clinics

Clinic protocol for review of patients: All patients were reviewed regularly for their general well-being and medication compliance. Eligible patients started on HU were reviewed fortnightly for the first four weeks, monthly for the next five months, and then every other month. Baseline investigations, including retroviral screening (RVS), full blood count (FBC), Hb quantification, serum electrolytes, urea and creatinine (EUCr), liver functions test (LFT) and transcranial doppler (TCD) scan were requested for all patients. Subsequently, patients on HU did FBC, EUCr, and LFT at four weeks, and the third month and sixth month with HbF were repeated at six months in accordance with the national guidelines. [21]

Study population

Children aged 2 to 15 years with SCA attending the haematology clinic and the consultant paediatric outpatient clinic who met the inclusion criteria for the study.

Inclusion criteria

Children aged 2 to 15 years with SCA who met the criteria for the commencement of HU therapy as outlined in the Standard Operating Protocol for Hydroxyurea Therapy.[21] These criteria include:

(i) ≥3 moderate to severe pain episodes in 12 months.

(ii) A history of acute chest syndrome (ACS) or symptomatic anaemia.

(iii) A history of stroke and contraindication to chronic transfusions or cases where chronic transfusion is not feasible.

(iv) A history of splenic sequestration crisis.

(v) Two successive borderline transcranial Doppler (TCD) velocities (170-199 cm/s) taken at least six months apart.

(vi) Abnormal TCD velocities (>200 cm/s) in children who have not commenced chronic blood transfusion.

(vii) Specific end-organ damage associated with SCA, such as ocular complications, priapism, and pulmonary hypertension.

(viii) Children whose parents/guardians provided informed consent.

(ix) Children older than 7 years who provided assent alongside parental consent.[22]

Exclusion criteria

(i) Children attending the Haematology Clinic who were already on HU.

(ii) Children with adverse clinical conditions specifically severe neutropaenia or serum creatinine more than 1.5mg/dl.

(iii) Children with other co-morbidities like Human Immuno-deficiency Virus infection, renal or liver impairment, congenital heart disease and malignancy.

Sample size

The calculation of sample size was based on the formula: [23]

$$n = \frac{(u+v)^2 (\sigma_1^2+\sigma_2^2)}{(\mu_1-\mu_0)^2}$$

Where n = minimum sample size

u is 1.96 at Type 1 error of 5%

v is 1.282 at 90% power

σ_1 is the standard deviation of haemoglobin before commencement of HU (from a previous study)[24]

σ_2 is the standard deviation of haemoglobin at 6 months of HU use (from a previous study)[20]

μ_1 is the mean haemoglobin at 6 months of HU use (from a previous study)[20]

u_0 is the mean haemoglobin before commencement of HU (from a previous study)[20]

$$n = \frac{(1.96+ 1.282)^2(1.1^2 + 1.3^2)}{(8.1-7.3)^2}$$

n = 10.51 x 2.9 /0.64 = 30.479/0.64

n =47.6 ≈ 48.

Assuming an attrition rate of 20% (10)

Proposed sample size = 48+10 = 58.

Fifty-eight children with SCA who met the inclusion criteria and the standard operating protocols for HU therapy, having been reviewed in the Haematology/ Consultant Outpatient Clinic, were consecutively recruited until the desired number was obtained.

Laboratory procedures for haematological parameters

Haematological parameters, including FBC, haemoglobin concentration, haematocrit, white blood cell count, platelet count, and haemoglobin F quantification, were carried out according to standard procedures.

Patient handling procedure

Recruited children were commenced on HU, at a dose of 10 - 15mg/kg/day, increasing by 5mg/kg/day every eight weeks (but not exceeding 35mg/kg/day) according to patients' haematological and clinical response. Precisely,

the dosage was adjusted based on the improvements in hematologic parameters (such as packed cell volume, white blood cell counts, and platelet counts) and clinical symptomatology while monitoring for adverse effects (such as thrombocytopaenia and leukopaenia). In the absence of adverse reactions, the dosage could be escalated up to 35 mg/kg/day. In the event of any adverse effects, HU was discontinued for 4-7 days and subsequently resumed at a previously tolerated dose. Notably, no adverse effects were documented in any of the children studied. A progress report was made on all study participants, and all clinical details were documented in the proforma.

Study proforma

The study proforma used for this research was designed to systematically collect clinical and haematological data on children with SCA undergoing hydroxyurea treatment. The proforma collected data on the biodata, past medical history, and physical examination findings, including anthropometry. Socioeconomic classification was done using the scheme of Ogunlesi *et al.* [25]

Data management and analysis

Data analysis: The data were processed with an IBM Statistical Package for the Social Sciences (IBM-SPSS) Data package (version 22.0) using descriptive and inferential statistics such as Chi-Square test, Yate's correction and Fisher's Exact test, Wilcoxon Signed Ranked test and Friedman's Two-Way Analysis of Variance test. P values <0.05 defined statistical significance.

Ethical considerations

Ethical approval for the study was obtained from both hospitals located in Abeokuta. Written informed consent was also obtained from the parents/guardians of all subjects and verbal assent from subjects older than seven who were eligible. The average time for administration of proforma, physical examination, and sample collection per participant was 45 minutes, and this did not interfere unnecessarily with the routine clinic.

Results

Fifty-eight children with SCA were consecutively enrolled into the study. Thirty-two (55.2%) of the subjects were males, while 26 (44.8%) were females with a male-to-female ratio of 1.2:1.

Sociodemographic characteristics (Table I)

The mean age was 9.12±3.61 years, with a range of 2 - 15 years. Twenty-seven (46.6%) were within the age group 6-10 years, while 19 (32.8%) were aged above 10 years. Thirty (51.7%) were of the Christian religion, 48 (82.8%) were of the Yoruba tribe, and 32 (55.2%) belonged to the socioeconomic classes IV and V.

Table I: Sociodemographic characteristics of the children with Sickle Cell Anaemia

Characteristics	Frequency (n = 58)	Percentage
Age group (years)		
≤5	10	17.2
6-10	27	466.
11-15	21	36.2
Religion		
Christianity	30	51.7
Islam	28	48.3
Ethnicity		
Yoruba	48	82.8
Hausa	4	6.9
Igbo	6	10.3
Socioeconomic class		
Class I	0	0
Class II	6	10.3
Class III	20	34.5
Class IV	28	48.3
Class V	4	6.9
Child's level of education		
Pre-nursery and Nursery	8	13.8
Primary	29	50.0
Junior Secondary	15	25.9
Senior Secondary	6	10.3

Past medical history (Table II)

Age at diagnosis: Of the 58 children with SCA, 23 (39.7%) were diagnosed on or before one year, while 14 (24.1%) were diagnosed at or after five years of age.

Vaso-occlusive crisis: In the preceding six months, 39 (67.2%) of the children had at least two episodes of vaso-occlusive crisis, while only four (6.9%) had not experienced any vaso-occlusive crisis.

Blood transfusions: Among these children, 21 (36.2%) had blood transfusions at least once in the preceding six months, with one out of this 21 (4.8%) transfused four times during the period.

Hospitalisations: Forty-nine subjects (84.5%) were admitted in the last six months with at least one form of sickle cell anaemic crisis and/or complications. The total number of hospitalisations among them was 100, with a median (IQR) of 2.0 (1.0). Among those who were hospitalised, 10 (17.2%) were hospitalised three or more times in the preceding six months.

Indications for admissions: Vaso-occlusive crises accounted for 45 (45.0%) of the total hospitalisations, followed by ACS 18 (18.0%), with one case each for chronic osteomyelitis, hepatic sequestration crisis and sickle cell nephropathy. Figure 1 shows the indications for admission.

Steady-state PCV: The steady-state PCV among the children studied ranged from 17% to 26%, with a mean of 21.3% ± 2.3. A majority (41; 70.7%) had their PCV in the 20-24% range.

Table II: Past medical history of children with sickle cell anaemia

Variables	Frequency (n = 58)	Percentage
Age at diagnosis (years)		
≤1	23	39.6
>1 to 4	21	36.2
≥5	14	24.1
Vaso-occlusive crisis in the previous 6 months		
0	4	6.9
1-2	30	51.7
≥3	24	41.4
Number of blood transfusions in the previous 6 months		
0	37	63.8
1	11	19.0
2	7	12.1
≥3	3	5.1
Number of hospitalisations in the last 6 months		
0	9	15.1
1	18	31.0
2	21	36.3
3	9	15.5
≥4	1	1.7
Steady-state Packed Cell Volume		
16-19	11	19.0
20-24	41	70.7
25-29	6	10.3

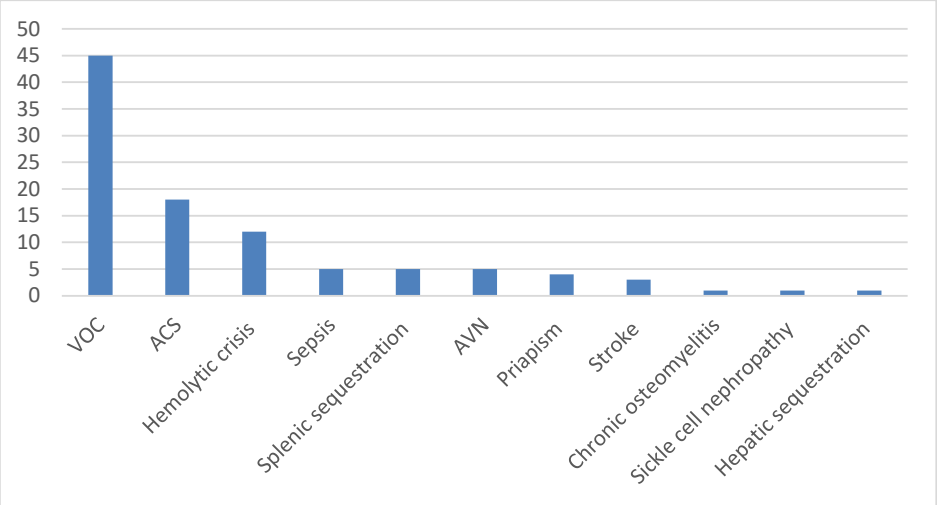

Figure 1: Indications for admission in the preceding six months

Pre- and Post-Hydroxyurea therapy physical findings

The weight and height ranges were 11–56kg and 87–164cm, respectively, with a mean weight of 25.9±8.2kg and a mean height of 129.9±17.9cm.

All the subjects' pre-therapy vital signs (temperatures, respiratory rates, and blood pressures) were within normal range. The axillary temperature and respiratory rates ranged from 36.2^{o}C to 37.2^{o}C and 20 to 28 cycles/minute, respectively. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were between the 50th and 90th centile, with values of 80–120mmHg and 50–76mmHg, respectively.

Pre-therapy, 40 (69.0%) children had their BMI-Z score within the normal range (-2 to 1) and 8 (13.8%) had severe thinness (BMI-Z score <-3) compared with the post-therapy state where 45 (77.6%) had their BMI-Z score within normal range, and 5 (8.6%) had severe thinness (p = 0.0723)

Also, 30 (51.7%) of the subject had hepatomegaly which ranged between 3 and 12cm (below the right costal margin) with median (IQR) of 6 cm (2cm) pre-therapy compared with 19 (32.7%), six months post-therapy (p = 0.128); and 9 (15.9%) had palpable splenomegaly which ranged from 2cm to 7cm with median (IQR) of 4cm (4cm) pre-therapy compared with 7 (12.0%), six months post-therapy (p = 0.299).

Indications for Hydroxyurea therapy

Figure 2 highlights the indications for the commencement of HU therapy. Sixty-eight indications were noted in the 58 subjects, as 10 had other indications besides VOC. The commonest indication for the commencement of HU was three or more VOC in the preceding six months (24; 35.3%) followed by high velocity (≥200cm/sec) transcranial Doppler (TCD) scan (13; 19.1%). Hepatic sequestration, sickle cell cardiomyopathy and chronic osteomyelitis were recorded in one subject each.

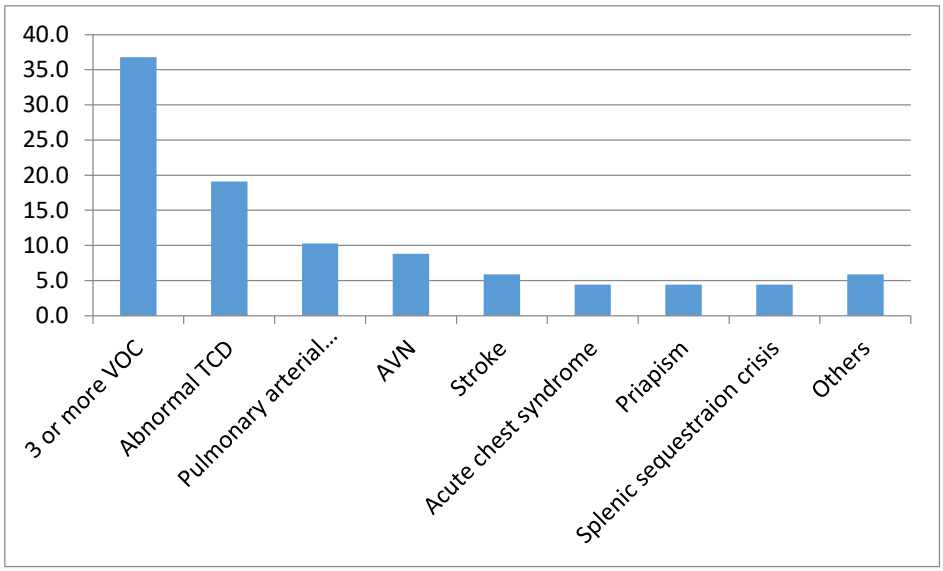

Figure 2: Indications for commencement of hydroxyurea therapy
VOC – Vaso-occlusive crises; TCD – Transcranial Doppler scan; AVN – Avascular necrosis.

Comparison of clinical parameters pre- and post-HU therapy

Table III shows the comparison of clinical parameters pre and post-HU therapy.

Vaso-occlusive crisis: Fifty-four (93.1%) children had at least one episode of vaso-occlusive crisis (VOC) six months before the commencement of HU therapy. This was reduced to 10 (17.2%) by the sixth month months post-HU therapy and with statistical significance (χ^2 = 64.45, df = 1, p<0.001). Also, 24 (41.3%) children had three or more VOC before the commencement of HU therapy compared with one (1.7%) child post-HU therapy (χ^2 = 82.56, df = 3, p<0.001).

Acute chest syndrome: Eighteen (31.0%) children had ACS six months prior to the commencement of HU compared with only 1 (1.7%) subject during the six months of HU therapy (χ^2 = 16.11, df = 1, p<0.001).

Hospitalisation: Forty-nine (84.5%) children had been hospitalised at least once during the six months preceding the commencement of HU therapy but by the end of the sixth month of HU therapy, only 5 (8.6%) children were hospitalised with statistical significance (χ^2 = 84.95, df = 1, p<0.001).

Blood transfusion: Twenty-one children (36.2%) had been transfused at least once during the six months before the commencement of HU therapy, while only one (1.7%) was transfused post-HU therapy (χ^2 = 20.25, df = 1, p = 0.001).

Sepsis: Confirmed sepsis was recorded in 5 (8.6%) children prior to HU therapy, while only 1 (1.7%) had sepsis post-therapy. This difference lacked statistical significance (χ^2 = 1.58, df =1, p = 0.21).

Stroke or priapism: Three subjects (5.2%) had a stroke, and 3 (5.2%) also had priapism during the six months preceding the commencement of HU therapy. During the six months of the use of HU therapy, none of the subjects had a new episode of either stroke or priapism.

Comparison of Haemoglobin F Values and Haematological Parameters Pre- and Post-Hydroxyurea Therapy

HbF values: Overall, there was a statistically significant difference in the median value of HbF pre-therapy and post-HU therapy (6.6 vs.15.9 respectively, p = 0.001). There was a positive median difference in all the participants as none

had the same HbF value pre- and post-HU therapy.

Haematological values: The pre-HU values of PCV, MCV and MCH showed a steady and consistent rise up to the end of the study at the sixth-month post-hydroxyurea therapy, which was statistically significant (p = 0.001). The reverse was the case with WBC count and platelets count, which showed a consistent decline with statistical significance (p <0.001). In contrast, MCHC values showed minimal decline with statistical significance (p < 0.001), as shown in Table IV.

Table III: Comparison of clinical parameters pre- and post-HU therapy

Parameter	Pre-HU n (%)	Post-HU n (%)	Statistics	p-value
Vaso-occlusive crisis (VOC)*				
0	4 (6.9)	48 (82.8)	82.56	0.000
1	15 (25.9)	5 (8.6)		
2	15 (25.9)	4 (6.9)		
≥3	24 (41.3)	1 (1.7)		
Acute chest syndrome*				
Yes	18 (31.0)	1 (1.7)	16.11	0.001
No	40 (69.0)	57 (98.3)		
Frequency of hospitalisation**				
0	9 (15.5)	53 (91.4)	84.95	0.001
1	18 (31.0)	5 (8.6)		
2	21 (36.3)	0 (0.0)		
≥3	10 (17.2)	0 (0.0)		
Frequency of blood transfusion**				
0	37 (63.8)	57 (96.6)	24.08	0.001
1	11 (19.0)	1 (1.7)		
>1	10 (17.2)	0 (0.0)		
Sepsis*				
Yes	5 (8.6)	1 (1.7)	1.582	0.21
No	53 (91.4)	57 (98.3)		
Stroke**				
Yes	3 (5.2)	0 (0.0)	0.24	0.001
No	55 (94.8)	58 (100.0)		
Priapism**				
Yes	3 (5.2)	0 (0.0)	0.24	0.001
No	55 (94.8)	58 (100.0)		

***Yates' Correction applied to any cell < 5 **Fisher's Exact test applied to cells <0**

Packed Cell Volume (PCV): The pre-HU therapy median (IQR) PCV value was 22.0% (3.9%), with a steady increase to 27.0% (3.5%) by the end of six months post-HU therapy, and this was statistically significant (p = 0.001).

Comparing the PCV values across the various months with each other using Friedman's Two-way analysis of variance, the PCV at one, three and six months

were all significantly higher than the pre-commencement PCV (p = 0.002, p< 0.001 and p<0.001 respectively). Also, the PCV at three months was significantly higher than the PCV at one month (p = 0.001), while the PCV at six months was significantly higher than those recorded at one and three months, respectively (p = 0.000).

Table IV: Comparison of haematological values before and after commencement of hydroxyurea

Parameter	At Commencement	At 1 month	At 3 months	At 6 months	Friedman's Analysis of variance	*p*-value
PCV (%)	22.0 (3.9)	22.9(3.8)	25.0 (3.8)	27.0 (3.5)	134.0	0.001
WBC (x 10^9/L)	16.7 (11.3)	14.6 (9.4)	11.5 (4.9)	9.7 (3.0)	112.8	0.001
Platelet(x10^9/L)	433.0 (188.3)	401.0 (150.0)	353.5 (180.3)	293.0 (164.3)	35.4	0.001
MCH (pg)	27.1 (3.4)	27.9 (3.3)	29.4 (4.9)	31.3 (4.3)	147.9	0.001
MCV (fl)	81.1 (11.1)	83.4 (10.9)	88.7 (10.3)	95.0 (12.9)	147.7	0.001
MCHC (g/dl)	33.0 (1.8)	33.2 (1.1)	32.8 (2.2)	32.4 (2.5)	33.9	0.001

Data are presented as Median (Interquartile range)

White Blood Cell (WBC) count: There was a steady decline in the total WBC count from the pre-commencement median (IQR) values of 16.7 × 10^9/L (11.3 × 10^9/L) to 9.7 × 10^9/L (3.0 × 10^9/L) at the sixth month after the commencement of HU, and this decline in WBC was statistically significant (p = 0.001). The WBC count at the sixth month was significantly lower than the WBC at three months, one month and pre-commencement (p<0.001).

Platelet count: The highest median value of platelets of 433.0 × 10^9/L (188.3 × 10^9/L) was observed at the pre-commencement point with sustained reduction of the values up to the end of the study at the sixth month [293 × 10^9/L (164.3 × 10^9/L)], and this was statistically significant (p = 0.001). The platelet count in the sixth month was lower than in the third month, but this was not statistically significant (p = 0.067). When the first-month value was compared with the pre-commencement value, it was also not statistically significant (p = 0.122).

Mean Corpuscular Haemoglobin (MCH): There was a steady rise in the MCH from the pre-commencement median (IQR) values of 27.1pg (3.4) to 31.3pg (4.3). This rise was statistically significant (p = 0.001). The MCH at one, three and six months were significantly higher than the pre-commencement MCH (p<0.001). Also, the MCH in the third and sixth months was significantly higher than at one month (p<0.001). In addition, the MCH in the sixth month was considerably higher than in the third month (p<0.001).

Mean Corpuscular Volume (MCV): The MCV values rose steadily from the pre-commencement median (IQR) 81.1fl (11.1) to 95.0fl (12.9) at the sixth-month post-HU therapy, and this rise were statistically significant (p = 0.001). The MCV in the first, third and sixth months were significantly higher than the pre-commencement MCV (p = 0.001 and p = 0.001, respectively). The MCV at three and six months was also significantly higher than at one month (p<0.001). In addition, the MCV at six months was significantly higher than that at three months (p<0.001).

Mean Corpuscular Haemoglobin Concentration (MCHC): There was a marginal decline in the MCHC pre-HU and post-HU therapy values from the median (IQR) of 33.0g/dl (1.8) to 32.4g/dl (2.5) with statistical significance (p = 0.001). The MCHC at the sixth month post-HU values was statistically significantly lower than that of the third, first and pre-commencement values (p = 0.037, p<0.001 and p<0.001 respectively). The value in the third month was lower than the first

month and pre-commencement significant (p = 0.012 and p = 0.003, respectively). The first-month values were marginally higher than the pre-commencement values but without statistical significance.

Discussion

This study reports the effects of Hydroxyurea treatment on the clinical and haematological profiles of children with SCA at two referral hospitals in Abeokuta, Nigeria. In this study, HU was observed to have positive effects on SCA outcomes. All the children on HU had a significant improvement in their clinical profile, as shown by a reduction in the frequency of VOC, ACS, blood transfusion and hospitalisation. There was a significant increase in the HbF values, PCV, MCV, and MCH, and a statistically significant decrease in the total WBC count, platelet count, and MCHC. The overall outcome of this study conforms with the findings from similar studies by Ofakunrin *et al.*[18] and Yahoudehou *et al.*[26] in Nigeria and Brazil, respectively.

This study shows that HU improved the clinical status of study subjects as there was an appreciable reduction in the frequency of VOC, ACS, hospitalisations and blood transfusion. The occurrence of other major complications of SCA, such as priapism and stroke, was also significantly reduced. The improved patient outcome observed in this study agreed with documented reports by earlier workers in Nigeria,[18] other African countries (Angola, Democratic Republic of Congo, Kenya and Uganda) by Tshilolo e*t al.* [20] and developed countries.[27]

The reduction in the frequency of blood transfusions and hospitalisations after HU therapy is similar to other studies. [13,18,27] This has been attributed to its ability to reduce VOC and ACS, which are common causes of hospitalisation, and its increasing effect on the PCV and ultimate reduction in transfusion rate.[28] This, in effect, will reduce the overall economic and psychosocial burden on the parents/caregivers and improve the quality of life of these patients and their caregivers.

This study demonstrated a significant increase in HbF with HU use, which was also in concordance with the findings of the earlier researchers.[18,20,26,29] The increase in the HbF production has been documented as the main mechanism of action of HU as it reduces the sickling process. The high HbF values have also been shown to correlate with reduced disease severity.[18,30] There was a consistent rise in the PCV, MCV and MCH values. This finding is in agreement with previous studies within and outside the country.[16,18-20] The increment in PCV decreases the need for blood transfusion in these patients, thereby increasing transfusion intervals. This was corroborated by the significant reduction in blood requirement in the present study.[28] The rise in MCV and MCH is not unexpected with HU therapy, which is noted to increase the haemoglobin content of RBC. Mean corpuscular volume has been used as an indicator for HU adherence in subjects with SCA. Those with low MCV, despite HU therapy, probably have poor compliance with the therapy. This is because the occurrence of macrocytosis is directly proportional to an increase in HbF.[31] The total WBC count, platelet count and MCHC showed a steady decline from the first month to the six-month post-HU therapy in the present study, and this finding correlates with similar reports.[16,18,20,32] hydroxyurea was reported to have myelosuppressive and cytoreductive properties, which may be responsible for the observed reduction in total WBC platelet count and MCHC. This mechanism has also been postulated to favour the decline in the frequency of VOC.[33] It is noteworthy that none of the children in the present study expressed features of toxicity

necessitating discontinuation of therapy in tandem with the findings of other researchers,[19,32] although continuous monitoring of the children on HU is continuous. Mean corpuscular haemoglobin concentration is affected by hydration status at the cellular level; hence, with dehydration (which is associated with VOC due to potassium and water efflux from the cell), there is an increase in MCHC, while HU, on the other hand, causes cellular hydration, thereby decreasing MCHC.[34]

The study has attempted to assess the effects of HU on the clinical status, HbF value and haematological profiles of SCA children and has demonstrated a beneficial impact on all the parameters assayed, giving further credence to the use of HU by healthcare workers managing SCA patients in resource-poor country like ours where facilities for a cure in the form of bone marrow transplant, is not readily available and accessible. The positive effects of HU documented so far may encourage and strengthen the caregivers, and promote its use in children with SCA before complications arise, thereby possibly improving the quality of life of affected children.

Conclusion

It is concluded that there were significant improvements in the clinical profiles of children with SCA on hydroxyurea therapy over six months. These improvements were noticeable as early as three months post-commencement of HU. Substantial improvements were also observed in the haematological profiles of children with SCA on HU therapy over six months.

Hydroxyurea should be globally adopted for managing SCA in children due to its proven clinical and haematological advantages. A multicenter study should be conducted to assess the effect of HU on SCA patients across various ethnic groups in Nigeria and to develop clinical practice guidelines for using HU based on this research finding.

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