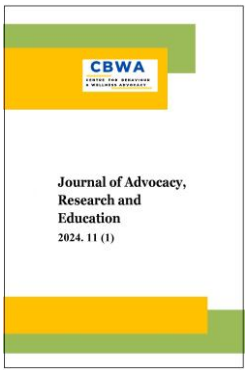
Publisher: Centre for Behaviour and Wellness Advocacy, Ghana
Co-publisher: Cherkas Global University, USA
Has been issued since 2014
ISSN 2410-4981. E-ISSN 2508-1055
2024. 11(1): 148-156

DOI: 10.13187/jare.2024.1.148

Journal homepage:
http://kadint.net/our-journal.html



Changes in Haematological and Clinical Parameters in Sickle Cell Disease Patients on Hydroxyurea: A Before and After Non-Experimental Retrospective Study

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Abstract

Sickle cell disease (SCD) poses a significant health burden globally, particularly in Africa, where prevalence rates are notably high. Hydroxyurea has emerged as a promising therapeutic agent for managing SCD, yet its effects on clinical outcomes in the Ghanaian context remain understudied. This retrospective study aimed to investigate changes in clinical and haematological parameters associated with hydroxyurea use in adolescents and adult patients living with sickle cell disease. A three-level retrospective review was conducted among 105 patients with sickle cell disease at the Ghana Institute of Clinical Genetics, Korle-Bu Teaching Hospital. Clinical and haematological information was retrieved six months before treatment, six months and 12 months after hydroxyurea therapy. A paired t-test was used to determine changes in haematological parameters before and after hydroxyurea therapy. The findings showed a significant increase in haemoglobin (Hb) and mean corpuscular volume (MCV) at six months. Only Hb increased significantly at 12 months. A significant reduction was observed in white cell count (WBC), platelet and retic count in the 6th month, but the changes from the 6th month to the 12th month were insignificant. An increase in foetal haemoglobin was observed in one patient at six months. Hydroxyurea significantly reduced the frequency of vaso-occlusive crises and hospitalisation. Clinicians should educate and recommend hydroxyurea to patients due to its positive clinical outcome.

Keywords: Sickle Cell Disease, Hydroxyurea, Clinical Outcomes, Haematological Parameters, Ghana.

1. Introduction

Sickle cell disease (SCD) is a global public health problem and the most predominant severe genetic haemoglobinopathy worldwide (Modell, Darlison, 2008; Piel et al., 2013). In Africa, where the burden is particularly high, over 200,000 children are born annually with the disease (Diallo,

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Received: 02 April 2024 Revised: 20 April 2024 Accepted: 23 April 2024 Published: 31 April 2024

Tchernia, 2002; Olowoyeye, Okwundu, 2020). In Ghana alone, SCD affects approximately 2 % of newborns, with 25 % to 30 % of the population being carriers of the gene (Edwin et al., 2011). It is characterised by frequent painful vaso-occlusive crises, haemolytic anaemia, and numerous complications such as acute chest syndrome, avascular necrosis, leg ulcers, renal damage, retinopathy, and stroke (Wankhade et al., 2013). Although haematopoietic stem cell transplantation offers a curative option, its limited availability and high cost render it inaccessible for many (Ikawa et al., 2019). Therefore, the management of SCD primarily relies on supportive measures, encompassing both pharmacological and non-pharmacological interventions to alleviate symptoms and mitigate complications (Asnani et al., 2019).

Hydroxyurea (HU) has emerged as a cornerstone medication for modifying the pathology of SCD, ameliorating clinical symptoms, and improving patient outcomes (Alvarez et al., 2012; Nevitt et al., 2017). Clinically, HU has demonstrated efficacy in reducing vaso-occlusive crises, hospital admissions, blood transfusions, acute chest syndrome, and organ damage (Silva-Pinto et al., 2013). Patients receiving HU exhibit haematological improvements, including increased foetal haemoglobin (HbF) levels, haemoglobin (Hb) levels, and mean corpuscular volume (MCV), along with decreased white cell count (WBC), platelet count, and reticulocyte count (Adewoyin et al., 2017). Moreover, the use of HU has been associated with enhanced quality of life, particularly in terms of physical functioning and emotional well-being among SCD patients (Badawy et al., 2017; Nwenyi et al., 2014; Thornburg et al., 2011). Despite its established efficacy, concerns have been raised regarding the accessibility, affordability, and safety of HU in low-resource settings, particularly in Africa (Yawn et al., 2014). However, research trials in Sub-Saharan Africa have demonstrated the safety, feasibility, and benefits of HU for SCD treatment (Tshilolo et al., 2019; Opoka et al., 2017).

Furthermore, HU was approved by Ghana's Food and Drugs Authority in 2018, and by 2023, more than 4,400 SCD patients had received HU. Notably, HU is now covered by Ghana's National Health Insurance Scheme (Nyonator et al., 2023). The adolescent and adult Sickle Cell Clinic at the Ghana Institute of Clinical Genetics, Korle-Bu, began utilising HU for SCD management in 2015. Despite the growing global interest in HU therapy for SCD management, there remains a notable gap in research specific to clinical and haematological parameters among adult SCD patients in Ghana. While studies from other regions have shown promising outcomes associated with HU use (Tarazi et al., 2021; Yang et al., 2022), extrapolating these findings to the Ghanaian population may not be appropriate due to variations in genetic backgrounds, environmental factors, and healthcare infrastructure. Therefore, this retrospective study of patients' clinical records was designed to investigate the changes in clinical and haematological parameters associated with HU use in adolescents and adults living with SCD. This study contributes to the global body of knowledge on HU therapy in SCD patients, particularly in resource-limited settings.

2. Materials and Methods

Study Design and Setting

This study was a retrospective review conducted among adolescent and adult SCD patients on HU at the Adolescent and Adult Sickle Cell Clinic, Ghana Institute of Clinical Genetics (GICG), Korle-Bu. The SCD clinic at GICG has over 25,000 registered patients. It is a day clinic that renders treatment services to SCD patients ages 13 years and older. Moreover, HU is one of the drugs used in clinics to manage sickle cell patients.

Study eligibility and sampling

Patients living with SCD aged 15 years and older enrolled on HU with at least six months of haematological and clinical records before starting HU therapy and who had completed 12 months of therapy with HU were included in the study. Patients who experienced side effects and were withdrawn from the medication before 12 months were excluded from the study.

Data collection

The Korle-Bu Teaching Hospital Institutional Review Board (KBTH-IRB) approved the study with ID number STC/IRB/000102/2021. Permission for data extraction was sought from the adult sickle cell clinic. Data were extracted devoid of personal identifiers. Data were extracted from the hospital records of patients who met the inclusion criteria using a data extraction tool. Data were collected at three-time points: six months before treatment with HU, six months, and 12 months post-HU treatment. The data extracted included patients' demographic characteristics, maximum

prescribed HU dosage, clinical (vaso-occlusive crisis, acute chest syndrome, blood transfusion and hospitalisation) and haematological parameters (Hb, HbF, WBC, mean corpuscular volume (MCV), platelet and reticulocyte count).

Data Analysis

Data were cleaned and cross-checked for completeness. Data were analysed using Stata version 16.0 statistical software. Continuous variables such as Hb, HbF, WBC, MCV, platelet and reticulocyte counts were summarised as means and standard deviation (SD). Categorical variables, such as clinical characteristics, were summarised as frequencies and percentages. To assess changes in haematological parameters, a paired t-test was used to compare differences in means of changes in haematological parameters before and after treatment with HU (Table 2). Furthermore, differences in proportions for clinical parameters, including the frequency of vaso-occlusive crises, acute chest syndrome, blood transfusion, and hospitalisation, were estimated using the z-test of proportions. This statistical test enabled the comparison of proportions between two-time points: before and after treatment with HU (Table 3). A significance level of 5% was adopted to determine statistical significance.

3. Results

Demographic characteristics of participants

Over the study period, there were 270 SCD patients who had been put on HU therapy. Out of the total 270 folders, 105 met the inclusion criteria. Hence, a total of 105 were finally selected for the study. The study flowchart is presented (Figure 1).

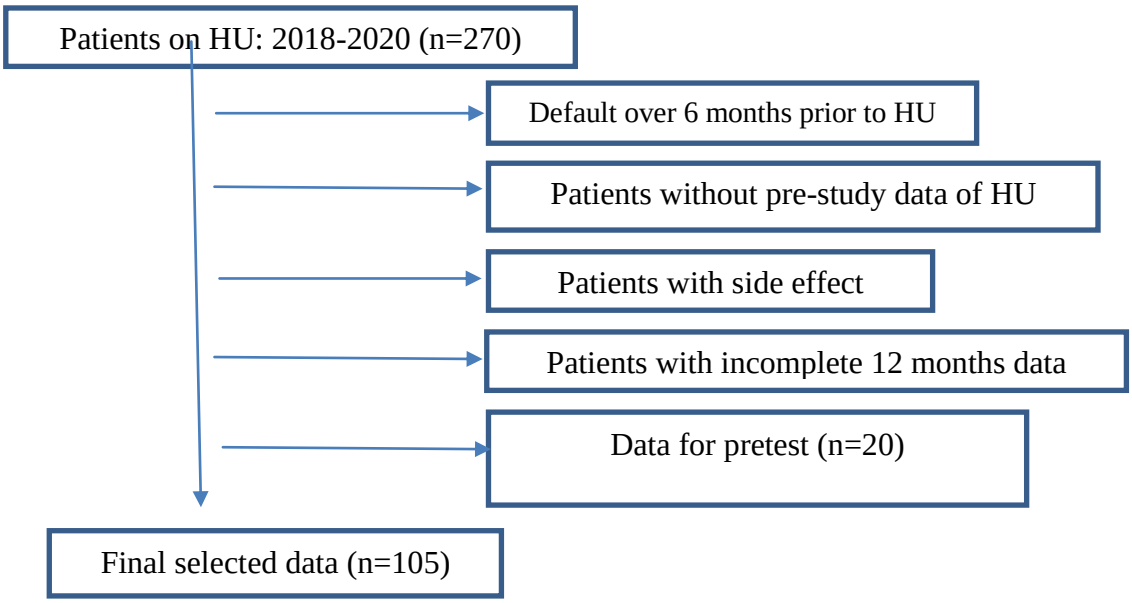

Fig. 1. A chart of the study flow

Out of the 105 patients included in the study, 56(53.8%) were females. Approximately two-thirds, 66(62.9%) of the study patients were between 20 and 39 years. Regarding the phenotype of patients, the majority, 94(89.5%) were HbSS. The average weight of the patients was 55.1 ± 12.5 kg. However, the mean weights of the adolescents and adults were respectively 46.2 ± 9.1 and 60.2 ± 11.3 (Table 1).

Table 1. Demographic Characteristics of SCD patients

Variables	Frequency (N)	Percentage (%)
Age		
<20	32	30.4
20-39	66	62.9

Variables	Frequency (N)	Percentage (%)
40-59	7	6.7
Subtotal	105	100.0
Sex		
Female	56	53.84
Male	49	47.15
Subtotal	105	100.0
Genotype		
Hb-Sß-THAL	2	1.9
Hb-SC	9	8.6
Hb-SS	94	89.5
Subtotal	105	100.0
Total weight (mean±SD)		
Adolescents (≤ 19 years)	46.2 ± 9.1	
Adults (≥ 20 years)	60.2 ± 11.3	

Changes in selected haematological parameters (Mean Hb, WBC, MCV, PLT and RET) after treatment with HU

The Hb concentration increased by 0.71g/dl from baseline to the sixth month, which was statistically significant at ($p < 0.001$). The WBC count decreased by -1.79 from baseline to 6 months post-treatment (Table 2). This drop was significant at $p<0.001$. However, the WBC increased from the sixth month to 12 months post-treatment by 0.58 $10^3/mm^3$. This difference was, however, not statistically significant ($p = 0.183$). Platelet count decreased from baseline to the sixth month by -32.91 $10^3/mm^3$. This change was significant ($p = 0.031$). However, an increase of 16.54 $10^3/mm^3$ was observed in the platelet count from the sixth to twelfth months. This change was not significant ($p = 0.338$).

MCV increased from the baseline to the sixth month by 9.38 μm^3. This increment was statistically significant ($p < 0.001$). There was, however, a slight decrease of 0.40 μm^3 in MCV from the sixth to the twelfth month. The change was not statistically significant ($p = 0.084$). Reticulocyte count decreased by -1.71% in the sixth month, which was significant ($p < 0.001$). However, a drop of 0.34% from the sixth to 12 months was not statistically significant.

Table 2. Haematological Parameters of Sickle cell patients at Pre-test, six- and 12-months Post HU Treatment (Paired t-test)

Variables	Pre-test (mean±SD)	6 M (mean±SD)	Change 0-6M	p-value	12 M (mean±SD)	Change 6M-12M	p-value
Hb (g/dL)	8.40±1.52	9.11±1.55	0.71	<0.001	9.31± 1.47	0.20	**0.021**
WBC ($10^3/mm^3$)	11.48±3.92	9.68±4.13	-1.79	<0.001	10.26±5.50	0.58	0.183
MCV (μm^3)	85.38±9.96	94.77±12.41	9.38	<0.001	94.36±11.87	-0.40	0.612
PLT ($10^3/mm^3$)	426.28±158.82	393.36±162.74	-32.91	0.031	409.90±196.35	16.54	0.338
Retic	8.76±5.43	7.05± 2.77	-1.71	<0.001	6.70±2.69	-0.34	0.112

Notes: Abbreviations: Hb – haemoglobin; WBC – white blood cells; MCV – mean cell volume; PLT – platelets.

Clinical parameters of SCD patients before and after treatment with HU

Out of the 105 sickle cell patients on HU, 68 (64.8 %) experienced a vaso-occlusive crisis at baseline, but this reduced to 20 (19.0 %) after treatment with HU at six months. This change was significant ($p < 0.001$). Acute chest syndrome reduced from 4 (3.8 %) at baseline to 1 (1.0 %) at six months after treatment. This change was not significant ($p = 0.174$). The frequency of blood transfusion reduced from 7 (6.7 %) pre-intervention to 3 (2.9 %) post-intervention at six months. This was also not statistically significant ($p = 0.195$). Hospitalisation also reduced from 38 (36.2 %) at baseline to 10 (9.5 %) at six months. This change was statistically significant at $P < 0.001$ (Table 3).

Table 3. Clinical Manifestations of SCD patients before and after treatment with HU (z-Test of Proportions)

Variables	Treatment with HU		Total	P-value
	Pre-test N (%)	Post-test N (%)		
Vaso-occlusive crises			45.07	<0.001
No	37 (35.2)	85 (81.0)		
Yes	68 (64.8)	20 (19.0)		
Acute chest syndrome			1.84	0.174
No	101 (96.2)	104 (99.0)		
Yes	4 (3.8)	1 (1.0)		
Blood transfusion			1.68	0.195
No	98 (93.3)	102 (97.1)		
Yes	7 (6.7)	3 (2.9)		
Hospitalised			21.23	<0.001
No	67 (63.8)	94 (90.5)		
Yes	38 (36.2)	10 (9.5)		

4. Discussion

This study aimed to evaluate the effect of HU on clinical outcomes among adolescents and adult SCD patients in Ghana. The study assessed the effect of HU on clinical and haematological outcomes among patients in the largest adolescent and adult SCD Clinic in Ghana. The sample size employed (n=105) is comparatively higher than most other studies on SCD and HU with sample sizes ranging between 24 and 128 (Adewoyin et al., 2017; Akingbola et al., 2019; Neves et al., 2012; Nwenyi et al., 2014; Pradhan et al., 2018; Sethy et al., 2018; Silva-Pinto et al., 2013; Singh et al., 2010; Yahouédéhou et al., 2018). This study demonstrates beneficial effects in both haematological and clinical parameters following HU use. HU increased Hb level, MCV, reduced WBC, Reticulocyte, and Platelet counts at six months and 12 months. This finding is similar to previous studies (Adewoyin et al., 2017; Akingbola et al., 2019; Neves et al., 2012; Pradhan et al., 2018; Sethy et al., 2018; Silva-Pinto et al., 2013; Singh et al., 2010; Yahouédéhou et al., 2018) in which HU significantly increased Hb level, MCV and reduced WBC, PLT count at 12 months.

At six months of HU therapy, the patients presented with a significant increase in Hb and MCV, along with a reduction in WBC and platelet counts. These findings are similar to previous studies in India and Brazil (Di Maggio et al., 2018; Singh et al., 2010b). However, reticulocyte counts were not reported by these authors. In our study, reticulocyte counts were reduced significantly at six months and maintained at 12 months. There was no significant difference in the white cell counts, platelet count and MCV at 6 and 12 months, similar to a study by Singh et al. (2010), suggesting that the changes seen in these parameters were maintained. This is not surprising since most patients were maintained on a fixed dose of HU. Only the Hb level increased significantly at 12 months, which was in agreement with most studies (Pradhan et al., 2018; Sethy

et al., 2018; Silva-Pinto et al., 2013). On the contrary, Singh et al. (2010) reported no significant increase in Hb after a year with a sample size of 24 patients.

A study in India and Greece (Singh et al., 2010; Voskaridou et al., 2010) reported a highly significant increase in MCV. Due to the relatively high cost of high-performance liquid chromatography (HPLC) for Hb quantification, most of the patients in this study could not pay for it. Only one patient performed a pre- and post-HPLC for HbF quantification, and this showed an increase in HbF levels after HU treatment. However, increased HbF concentration is only one mechanism of HU action in SCD. This finding is supported by Singh et al. (2010), indicating an excellent response to HU even without a significant change in HbF.

The frequency of vaso-occlusive crisis and hospitalisation was reduced significantly in this study. This was similar to a study conducted in India (Pradhan et al., 2018) that observed that the frequency of blood transfusion and acute chest syndrome was reduced by HU in this study, but these reductions were not statistically significant. This might be a result of very few patients who experienced acute chest syndrome or who received transfusion before they were started on HU.

5. Conclusion and Limitations

HU treatment resulted in a beneficial reduction in WBC, Platelet and Reticulocyte count and increased Hb level and MCV among the patients. Clinically, HU reduced the frequency of vaso-occlusive crises, acute chest syndrome, blood transfusion and hospitalisation. HU was generally safe in our cohort of patients.

The study's retrospective nature posed a limitation, as not all patients had complete data for all parameters, particularly for reticulocyte counts, potentially affecting the generalisability of the findings. Additionally, the study did not analyse the results based on the doses HU patients received or differentiate between the types of SCD. These variables are known to influence treatment response and clinical outcomes.

6. Implications

This study supports the continued use of HU therapy for treating SCD in Ghana by demonstrating its efficacy in improving haematological parameters and clinical outcomes among adolescent and adult patients. These findings may inform policy decisions and guidelines for managing SCD at national and regional levels.

Future research should consider stratifying analyses based on the doses of HU administered and differentiating between the various subtypes of SCD. Future research should also adopt a prospective study design with longitudinal follow-up to ensure sustained treatment effects over time in Ghana and other countries with similar health systems.

7. Declarations

Ethics approval and consent to participate

The KBTH-IRB granted ethics approval for the study (STC/IRB/000102/2021).

Consent for publication

All authors read and approved the final version of the manuscript for publication and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Availability of data and materials

The data supporting this study will be made available upon reasonable request to the corresponding author (andrews.druye@ucc.edu.gh).

Conflict of interest statement

The authors do not have any personal or financial interest in this study.

Funding

The study was funded by the West Africa Genetics Medicine Center.

Authors' contributions

AAO and HAB conceptualised the study. AAO and HAB designed the study with input from DD, AAD and IAK. AAO extracted data from patient folders. IS, DD, AAD and HAB analysed and interpreted the data. AGM, AAO and HAB drafted the initial manuscript. EO, WG, AAD and IAK contributed to the revision and finalisation of the manuscript. All authors read and approved the final version of the manuscript.

8. Acknowledgements

This study was supported in part by a Postgraduate Fellowship from the West African Genetics Medicine Centre (WAGMC). We acknowledge Akosua Nyarko Kissi, the Records Staff of GICG, and Mr. Kwame Asante for assisting in data extraction.

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