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ORIGINAL ARTICLE

The Role of Hydroxyurea and the Clinical Outcome of Paediatric Sickle Cell Disease Patients in a Tertiary Hospital in North-Western Nigeria

Muhammad HA,[1] Suleiman AG,[2] Umar AA,[2] Sufiyan MB.[2]

[1]The MBBS Training Programme, College of Medical Sciences, Ahmadu Bello University Zaria, Kaduna State, Nigeria

[2]Department of Community Medicine, Ahmadu Bello University Zaria, Kaduna State, Nigeria

Keywords

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Haemoglobin;

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ABSTRACT

Background: Sickle cell disease (SCD) is a common condition in Nigeria that is associated with high morbidity and mortality among children. The use of hydroxyurea (HU), a disease-modifying agent that induces the synthesis of foetal haemoglobin, is limited by efficacy and safety concerns. This study aimed to assess the relationship between the use of HU and the frequency of adverse clinical events among paediatric SCD patients at a tertiary hospital in Northwestern Nigeria.

Methods: Using a retrospective cohort study design, a pro forma was used to extract data from 192 medical records of patients on HU therapy, including sociodemographic characteristics, pattern of HU use and adverse clinical events before and after the initiation of HU. For each of these adverse clinical events, incidence rates (IRs) and incidence rate ratios (IRRs) were calculated and assessed for statistical significance.

Results: During the study period, patients on HU were 13 times less likely to experience vaso-occlusive crisis (IRR=0.07, 95%CI: 0.05–0.12) and six times less likely to require hospital admission (IRR=0.16, 95%CI: 0.11–0.22). The use of HU was associated with an increase in patients' mean packed cell volume (3.2%, t191=8.222, P<0.01). Starting HU was not associated with significant changes in the prevalence of therapy-related side effects (8.9% versus 12.5%, x2=1.338, P=0.247).

Conclusion: Use of HU was associated with significant reductions in the incidence of all adverse clinical outcomes. There is a need for wider studies to further validate these findings, address the limitations of retrospective designs, and understand the factors limiting the wider use of HU.

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Correspondence to:
Dr. Auwal Suleiman Garba,
Department of Community Medicine, Faculty of Clinical Sciences,
College of Medical Sciences, Ahmadu Bello University Zaria,
Kaduna State, Nigeria.
Email: agsuleiman@abu.edu.ng

INTRODUCTION

Sickle cell disease (SCD) is a generic name for a group of inherited haemoglobin disorders characterized by abnormal sickle-shaped red blood cells, the presence of which leads to diverse clinical manifestations of the disease.[1] In Nigeria, the commonest variant is the homozygous haemoglobin S type (HbSS), acquired when an individual inherits an abnormal haemoglobin S gene from both parents.[1–3] The disease is characterized by episodes of painful crises due to vascular occlusion, anaemia from heightened destruction or sequestration of red blood cells, increased susceptibility to infection, chronic organ damage, and a higher risk of premature death.[4–6]

In Nigeria, the prevalence of HbSS among children aged 6-59 months is approximately 0.9%, but the estimated prevalence at birth is as high as 1.2%.[7,8] Every year, approximately 200,000 children are born with SCD, more than half of whom die before the age of five years.[9] The mortality rate among children under the age of five years who are born with SCD is 490 per 1000 live birth, about four times higher than that of children born with homozygous normal haemoglobin A (HbAA).[7]

Hydroxyurea (HU) is a myelosuppressive antineoplastic drug first approved in 1967 for the treatment of chronic myeloid leukaemia, but was soon discovered to induce the synthesis of haemoglobin F, a far more efficient oxygen carrier than haemoglobin S.[4] Thus, in 1998, HU received another approval for the treatment of sickle cell anaemia (SCA) as a disease-modifying agent.[4] Presently, HU is widely used in high-income countries with significant success, causing a marked reduction in the number of painful episodes, hospitalizations, and blood transfusions among patients, with attendant improvement in overall quality of life.[10]

In Nigeria, the National Guideline for the Control and Management of Sickle Cell Disease allows limited use of HU in patients with SCD.[1] According to the guidelines, patients may only be prescribed HU if they experience up to five crises per year, have abnormal trans-cranial Doppler velocity (above 200 cm/s), suffer from acute chest syndrome, or have had a stroke.[1] Patients with 3-4 crises per year may be considered if they have sufficient neutrophil or platelet count.[1] The use of HU is limited by several barriers stemming from providers and patients, including a lack of expertise among care providers, unclear clinical guidelines, fear of side effects, and doubts about efficacy.[11,12] Some patients have also expressed concerns regarding the cost of the drug, monitoring requirements, intake frequency, and side effects associated with the drug.[10,13]

While several carefully designed studies have been conducted to assess the efficacy and safety of HU in Nigeria, very few appear to have come from the North-western region,[10,14–17] the largest geopolitical region in the country with an estimated population of over 60 million. Previous attempts to investigate HU as a disease-modifying agent in SCD patients were

complicated by limited sample size, as relatively few patients were on HU therapy.[18] The aim of this study was to examine the role of HU as a disease-modifying agent and the incidence of adverse clinical events among paediatric patients with SCD in one of the largest tertiary hospitals in Northwestern Nigeria.

METHODOLOGY

Study area

The study was conducted at the Department of Paediatrics, Ahmadu Bello University Teaching Hospital (ABUTH) Zaria. The hospital is one of the pioneer hospitals in North-western Nigeria and serves as a referral centre for patients in the region. The Department provides specialized care to both in-patients on admission and out-patients through the paediatric outpatient clinic (POPD). Paediatric SCD patients are primarily managed by the Haemato-oncology Unit of the Department until they reach the age of 18 years when they are transferred to the Department of Haematology.

Study design

This was a retrospective cohort study among paediatric SCD patients managed by the Haemato-Oncology Unit of ABUTH Zaria. A number of these patients were placed on HU therapy for various indications, with some of them being on HU for many years at the time of the review.

Study population

The medical records were retrieved and reviewed to determine if they belonged to an SCD patient aged 2–17 years at the time of the review. The records must have spanned at least 24 months of follow-up, of which at least 12 months must be a period before the start of HU therapy to allow for a before and after comparison. Patients whose files contained extensive records covering several years of follow-up were also included. However, the focus of the review was limited to a maximum of 24 months before and 24 months after the start of treatment. Patients with coexisting medical conditions and those whose folders contained significant missing information were excluded.

Data extraction

The data extraction was conducted between the 8th and 20th of March 2022. All HU-designated medical records were retrieved from POPD and assessed for eligibility. A structured pro forma developed specifically for the study was used to extract the required information, including socio-demographic characteristics, pattern of use of hydroxyurea, adverse clinical events and documented side effects. The data was transferred to a Microsoft Excel spreadsheet for storage and management. Daily reviews were conducted until all available records were retrieved and assessed for eligibility.

Statistical analysis

The data was analysed using IBM SPSS Statistics (version 25.0) and Microsoft Excel (2016). Quantitative variables were analysed and summary statistics were reported as median (IQR). The categorical variables were presented in frequency distribution tables. A paired sample T-test was used to check for the difference between the mean packed cell volume (PCV) before and after HU initiation. The same test was

used to check for differences in the mean HU dose at the beginning and end of the review. A chi-square homogeneity test was used to compare the proportion of patients who experienced side effects before and after the start of HU. For statistical decision-making, a *p*-value less than 0.05 was considered statistically significant. To compare the risks of adverse clinical events before and after starting HU, the incidence rates (IRs) of such events were calculated before and after the start of HU. The same IRs were then used to calculate the incidence rate ratio (IRR):[19]

$$Incidence\ Rate\ (IR) = \frac{Number\ of\ events\ of\ interest\ (e_i)}{Total\ person{-}time\ of\ observations\ (n_i)} \quad (1)$$

$$Incidence\ Rate\ Ratio\ (IRR) = \frac{IR_{after\ HU\ therapy}}{IR_{before\ HU\ therapy}} \quad (2)$$

The IRR is a measure of relative risk, the value of which may be less than or greater than unity. When calculated this way, an IRR of more than 1 implies that the exposure (or intervention) is a risk factor, whereas an IRR of less than 1 implies that the exposure is a protective factor.[19] For decisions regarding IRRs, 95% Confidence Intervals (CIs) were calculated using the following formula:[20]

$$95\%\ CI_{IRR} = e^{(ln\ IRR \pm 1.96SE)} \quad (3)$$

Where *e* is the exponential and SE is the standard error of IRR, defined as:[20]

$$SE_{ln\ IRR} = \sqrt{\frac{1}{e_1} + \frac{1}{e_2}} \quad (4)$$

Where e_1 and e_2 are the number of adverse events before and after the start of HU. Thus, an IRR for a given event of interest was considered statistically significant if its 95% CI did not contain unity.

Ethical considerations

Ethical approval for this study was obtained from the Ahmadu Bello University Teaching Hospital Health Research Ethics Committee (NHREC/TR/ABUTH-NHREC/01/02/23).

Permission to access the medical records was obtained from the head of the Department of Paediatrics and the Chief Consultant of the Haemato-Oncology Unit of the department. All information retrieved was treated as confidential and the review did not attempt to collect any identifying information such as names, hospital numbers and contact details of the patients.

RESULTS

A total of 192 medical records met the eligibility criteria and were included in the review. Table 1 shows the socio-demographic characteristics of the SCD patients, the majority of whom were children (median age of 9 years). About half were males (57.3%) and the majority were Muslims (87.0%) from Hausa ethnic background (83.3%). Nearly all of them were diagnosed during infancy (96.4%), and in terms of their genotypes, the majority were HbSS (83.3%). (Table 1)

Table 1: Socio-demographic characteristics of paediatric SCD patients on HU therapy in ABUTH Zaria (n=192)

Variable	Frequency	Percent
Age group (years)		
2.0 – 5.9	60	31.3
6.0 – 9.9	57	29.7
10.0 – 13.9	64	33.3
14.0 – 17.9	11	5.7
Median (IQR)	9.0 (5.5–12.0)	
Sex		
Male	110	57.3
Female	82	42.7
Ethnicity		
Hausa	160	83.3
Igbo	5	2.6
Yoruba	8	4.2
Others	19	9.9
Religion		
Muslim	167	87.0
Christian	25	13.0
Age at diagnosis (months)		
Less than 6	5	2.6
6 – 11	180	93.8
12 – 17	6	3.1
18 – 24	1	0.5
Median (IQR)	6 (6–9)	
Genotype		
HbSS	162	84.4
HbSS+F	20	10.4
HbSC	10	5.2

ABUTH: Ahmadu Bello University Teaching Hospital, SCD: Sickle Cell Disease, HU: Hydroxyurea, IQR: Inter-quartile Range

Follow up

The mean duration of follow-up before and after the start of HU therapy was 22.4 (±3.2) months and 23.9 (±0.9) months, respectively. The mean duration of follow-up before HU therapy was slightly but significantly shorter than the mean duration of follow-up after starting HU therapy (Mean difference=1.5 months, t_{191}=6.198, P<0.001).

Dose of Hydroxyurea

The doses of HU administered to the patients were reviewed to determine if changes were made at the end of the review compared with when HU therapy was started. The mean dose at the commencement of HU therapy was 14.25 (±2.25) mg/Kg, whereas the mean dose of HU at the end of the review was 16.95 (±2.75) mg/Kg. There was a small, but statistically significant difference between the two mean doses (2.70 mg/Kg, t_{191}=10.575, P<0.001).

Table 2 shows the pattern of HU therapy among paediatric SCD patients in ABUTH Zaria. Half of the patients started HU therapy between the ages of 2 and 4, with a median of 3.8 years. Over half of the patients had been on HU therapy for at least 4 years, and the proportion of those who discontinued it at the time of the review was just 8.3%. The most common indications for HU therapy were recurrent vaso-occlusive crises, anaemic crises, and osteomyelitis. (Table 2)

Packed cell volume

The mean PCVs of patients before and after starting HU therapy were 20.0% (±3.4%) and 23.2% (±3.6%), respectively. The difference in the mean PCV before and after starting HU therapy was statistically significant (Mean difference=3.2%, t_{191}=8.222, P<0.001).

Adverse clinical events

Table 3 assesses and compares the rates of adverse clinical events among paediatric SCD patients before and after starting HU therapy. All events before and after the start of HU therapy were standardized to a period of observation equivalent to one year (i.e. 192 person-years). In general, the rates of adverse clinical events before the start of HU therapy were significantly higher than those after the start of HU therapy, with patients experiencing marked reductions in the rates of adverse clinical events. For instance, the rate of hospital admission, which was 1.17 times per patient per year before the start of HU therapy, reduced to 0.18 times per patient per year after starting HU (about 6.5 times risk reduction). The highest reduction was observed in the rate of vaso-occlusive crises, which reduced from an average of 1.48 times per person per year to 0.11 times per person per year (more than 13-fold risk reduction).

Side effects

Before the start of HU, the only documented side effect among the patients was iron overload, observed in 17 patients (8.9%). No side effects were reported in relation to the use of other therapies such as folic acid, proguanil and penicillin. However, after starting HU, 24 patients (12.5%) reported various side effects, including nail changes (16; 66.7%), skin rashes (6; 25.0%) and diarrhoea (2; 8.3%). Overall, the proportion of patients who experienced any therapy-related side effects before starting HU therapy was not significantly different from the proportion of patients who experienced any side effects after starting HU (8.9% versus 12.5%, χ^2=1.338, P=0.247).

DISCUSSION

This review was conducted to assess the effect of HU therapy on adverse clinical events among paediatric SCD patients in ABUTH Zaria. The majority of patients were children with a median age of 9 years. In a similar study among paediatric SCD patients in Jos, Northcentral Nigeria, the mean age of the patients was 8.5 years.[17] This is expected, given that paediatric clinics usually transfer their patients to adult clinics when they reach adulthood.

Table 2: Pattern of HU therapy among paediatric SCD patients in ABUTH Zaria (n=192)

Variable	Frequency	Percent
Age at commencement of HU therapy (years)		
Less than 2	7	3.6
2.0 – 3.9	96	50.0
4.0 – 5.9	57	29.7
6.0 – 7.9	15	7.8
8.0 – 9.9	8	4.2
10 and above	9	4.7
Median (IQR)	3.8 (2.5–5.0)	
Duration of HU therapy (years)		
1.0 – 1.9	6	3.1
2.0 – 3.9	73	38.0
4.0 – 5.9	63	32.8
6.0 – 7.9	50	26.1
Median (IQR)	4.0 (3.0–6.0)	
Reason for HU therapy		
Recurrent vaso-occlusive crises	77	40.1
Recurrent anaemia	42	21.9
Chronic osteomyelitis	17	8.9
Stroke	12	6.3
Acute chest syndrome	10	5.2
Iron overload	9	4.7
Multiple reasons	8	4.2
Avascular necrosis of the head of femur	7	3.6
Request by parents	5	2.6
Priapism	3	1.6
Voluntary counselling	2	1.0
Current status of HU therapy		
Still on HU	176	91.7
Have stopped HU	16	8.3

ABUTH: Ahmadu Bello University Teaching Hospital, SCD: Sickle Cell Disease, HU: Hydroxyurea, IQR: Inter-quartile Range

The review noted that the majority of the patients were diagnosed with SCD during infancy, consistent with a previous report from Northern Nigeria, which reported over half of the SCD children in the study were diagnosed during infancy.[21] However, in two studies conducted in Enugu and Oyo States (Southern Nigeria), the median age at diagnosis was significantly higher (24 months).[22,23] Age at diagnosis is influenced by several factors, including variants of the disease, environment, socioeconomic status, and familiarity with the disease.[23,24] These factors may continue to determine the age at diagnosis because newborn screening for SCD is still not widely available in Nigeria.

In this review, the dose of HU administered to patients was in the range of 14-17 mg/kg. This aligns with the National Guideline for the Control and Management of Sickle Cell Disease, which recommends a starting dose of 15 mg/kg and advises against any further increase unless clinical response remains unsatisfactory.[1] This was done to avoid dose-dependent side effects of the drug, including myelosuppression.[1] However,

clear indications exist that even lower doses of HU can have therapeutic effects.[25] A study conducted to determine the non-inferiority of low-dose HU (10mg/Kg) to moderate-dose HU (20mg/Kg) in preventing secondary stroke among SCD patients in Kano State, North-western Nigeria, observed that the risk of secondary stroke or death in the low-dose HU group was not significantly different from that in the moderate-dose HU group (IRR=0.98, 95% CI: 0.32–3.00).[25] This is a significant development, particularly for health systems in resource-constrained countries where patients struggle to pay for the drug.

In this review, the most common indications for HU were recurrent vaso-occlusive crises, anaemic crises and osteomyelitis. This pattern agrees with the provisions of the National Guideline, which recommends that only patients with recurrent crises or life-threatening conditions be placed on HU therapy.[1] Elsewhere, different recommendations are obtainable. The National Heart, Lung, and Blood Institute recommends offering HU therapy to all SCA patients as early as 9 months.[26] The review also observed a slight but significant increase in the mean PCV level of patients after HU initiation. This is similar to findings from previous studies in Nigeria that showed a small but significant increase in PCV (or haemoglobin) after starting HU.[10,17,26] This may be expected, given that HU is a disease modifier rather than a myeloproliferative agent.

Our study found that the use of HU among paediatric patients was associated with a significant reduction in the risk of adverse clinical events. This is consistent with the known therapeutic effects of HU, which induces the production of HbF, a far more efficient haemoglobin than HbS. In addition, HU improves cellular hydration, limits the interaction of sickle erythrocytes with the vascular endothelium, and acts as a nitric oxide donor.[2] The additive effect of all these factors may lead to improved blood flow, better oxygenation, and reduced vaso-occlusive tendencies.[2] Some studies from within and outside Nigeria have shown that the use of HU is associated with a significant reduction in the rate of adverse clinical events. [4,10,17,26]

The review observed that the use of HU during the 24-month follow-up did not significantly increase the proportion of paediatric SCD patients who experienced any side effects, even though the side effects experienced before and after the start of HU therapy were not the same. Interestingly, none of the reported side effects were severe enough to warrant discontinuation. This is similar to the findings from Jos, North-central Nigeria, where paediatric patients commenced on HU reported only mild gastrointestinal symptoms after 12 months of follow-up.[17] Similarly, a large multicentre study conducted in Nigeria observed no significant association between experience of HU-related side effects and discontinuation of therapy, as most respondents claimed they did not experience any severe side effects due to HU.[13]

Despite concerns of liver toxicity among patients on HU therapy, a study among paediatric patients placed on HU therapy for at least 12 months showed no significant changes in the mean level of liver enzymes before and after starting HU therapy.[27] In contrast, findings from a nationwide study in Nigeria indicated that some patients stopped taking HU because of side effects which often includes neutropenia, and low platelet count.[28] This emphasizes the need for client education, adequate dosing, and proper monitoring, because most of the side effects associated with HU are reversible and may not occur again if therapy is stopped and recommenced at a lower dose.[28]

This review is not without limitations, and being a retrospective study, the study's findings would be affected by the quality of the review process, the problem of missing data, and the quality of documentation. We minimized this challenge by adopting a uniform pro forma for the data extraction. However, information that was either missing or incorrectly entered would still affect our study. As other studies often report other markers of disease and well-being in the context of HU such as HbF levels and mean corpuscular haemoglobin (MCV) of patients, our study is limited by what was routinely done and readily available in our setting. Similarly, medical folders that were no longer kept in the POPD at the time of the review, either because the person was deceased or for any other reason, could introduce a selection bias. In our setting, it is typical for patients to sometimes engage in self-care at home or visit a private care provider despite maintaining regular clinic follow-ups at the hospital. The hospital records would not have information regarding what happened during such events.

Our findings may also be susceptible to confounding because, over time, SCD patients may experience improvement in their symptoms regardless of whether they are taking HU or not. This could result from growth and adaptation, education from repeated counselling and the effect of other routine interventions like nutrient supplementation, malaria chemo-prophylaxis, and vaccination. This is especially relevant in our study, given that all our patients were first observed without HU for up to two years before they were then observed on HU for another two years. However, given the magnitude of the risk reductions observed in this study and the diverse age groups of the paediatric patients, it is unlikely that these confounders would account for the kind of changes observed in this study.

Table 3: Adverse clinical events before and after starting HU therapy among paediatric SCD patients in ABUTH Zaria (n=192)

Event	Before HU		After HU		IRR	95% CI	
	Number of Events (per 192 person-years	IR	Number of Events (per 192 person-years	IR		Lower	Upper
Hospital admission	225	1.17	35	0.18	0.16	0.11	0.22
Transfusion event	154	0.80	40	0.21	0.26	0.18	0.37
Vaso-occlusive crisis	285	1.48	22	0.11	0.07	0.05	0.12
Anaemic crisis	192	1.00	23	0.12	0.12	0.08	0.18
Severe infection	237	1.23	24	0.13	0.10	0.07	0.15
Stroke	36	0.19	9	0.05	0.25	0.12	0.52

ABUTH: Ahmadu Bello University Teaching Hospital, HU: Hydroxyurea, SCD: Sickle Cell Disease, IR: Incidence Rate, IRR: Incidence Rate Ratio, CI: Confidence Interval.

CONCLUSION

This review has demonstrated significant association between use of HU therapy and decreased incidence of adverse clinical events such as vaso-occlusive crisis, anaemic crisis, severe infection, hospital admission, blood transfusion, and stroke among paediatric patients with SCD. It is recommended that wider multicentre studies be carried out to further validate these findings, address the limitations associated with retrospective studies and understand the immediate and remote factors that limit the use of HU among paediatric SCD patients in Nigeria.

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Author's contribution: HMA – Conceptualisation, data collection and review of manuscript. SAG – Conceptualisation, study design, data analysis, drafting and review of manuscript. UAA – Data analysis and review of manuscript. MSB – Data analysis and review of manuscript.

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