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Original Research

Hydroxyurea therapy in sickle cell disease: knowledge and prescription patterns among care providers in a low-and middle-income setting

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Abstract

Background: Hydroxyurea is a safe, effective, and well-tolerated disease-modifying therapy for patients with sickle cell disease (SCD), leading to reduced morbidity, mortality, and an improved quality of life. However, its underutilization, driven by inadequate knowledge and variability in use among SCD care providers, may limit its benefits. This study assessed the knowledge and prescription patterns of hydroxyurea among SCD care providers in Jos, Nigeria.

Methodology: A cross-sectional survey of 132 physicians managing SCD was conducted to collect data on socio-demographics, hydroxyurea knowledge, and prescription patterns using a proforma. Knowledge was assessed using 17 questions (maximum score: 17). Scores above 12 (50th percentile) were classified as "good," while scores of 12 or below were categorized as "poor." Prescription patterns were evaluated against the National Institutes of Health (2014) and British Society for Haematology (2018) guidelines. Data were analyzed using descriptive and inferential statistics.

Results: Sixty-seven (50.8%) of the 132 physicians had inadequate knowledge of hydroxyurea's clinical benefits and safety. Only 35 (26.5%) were aware of available treatment guidelines, and 32 (24.2%) had ever prescribed hydroxyurea. Among prescribers, nine (28.1%) used inappropriate criteria to initiate treatment and six (18.8%) prescribed below recommended doses. The median maximum daily prescribed dose was 750mg, whereas five (15.6%) physicians did not exceed 200mg, irrespective of patient weight. Treatment guidelines were not followed by 25 (78.1%) of prescribers.

Conclusion: This study revealed a high prevalence of inadequate knowledge and inconsistent hydroxyurea prescription practices among SCD care providers. Targeted training is essential to enhance hydroxyurea utilization and ensure adherence to standardized treatment guidelines, ultimately improving patient outcomes.

Keywords: Hydroxyurea; Sickle Cell Disease; Knowledge; Prescription Practices; Low Middle-Income Settings; Nigeria.

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Introduction:

Sickle cell disease (SCD) is a common inherited haemoglobinopathy caused by mutations in the beta-globin gene, resulting in the production of abnormal hemoglobin S (HbS). Individuals with homozygous mutations (HbSS) experience chronic haemolysis and recurrent vaso-occlusive crises, which lead to ischaemic tissue injury and life-threatening complications. Under hypoxic conditions, HbS polymerizes, causing erythrocytes to become rigid, adhesive, and prone to premature destruction. [1-3]

Globally, an estimated 300,000 infants are born with SCD annually, with over 75% in sub-Saharan Africa. Nigeria, the Democratic Republic of Congo, and India together account for nearly half of the global burden. [4-5] Despite ongoing efforts to improve survival, childhood mortality remains high in resource-limited settings due to inadequate healthcare access and complications such as invasive pneumococcal disease. [5] SCD is a debilitating disorder associated with significant morbidity, reduced quality of life, and early death, particularly in untreated cases. [6]

Hydroxyurea, a safe and effective disease-modifying therapy, has been shown to reduce vaso-occlusive crises, acute chest syndrome, and transfusion requirements, thereby improving survival and quality of life in both children and adults with SCD. [7-10] It is administered as a single daily oral dose, and its primary mechanism of action is the induction of foetal haemoglobin (HbF), which inhibits intracellular HbS polymerization and prevents the sickling process within erythrocytes. [11] Additional mechanisms include lowering neutrophil and platelet counts, reducing inflammatory markers, increasing mean corpuscular volume (MCV) for improved erythrocyte flexibility and rheology, and potentially releasing nitric oxide for vasodilation. [11] Common side effects include myelosuppression (manifesting as neutropenia, thrombocytopenia, or anaemia), mild gastrointestinal disturbances, and skin/nail changes, thereby necessitating regular blood count monitoring. [11] Several national and international guidelines, including those from the National Institutes of Health (NIH), British Society for Haematology (BSH), and Nigerian health authorities, outline dosing protocols, side effect management, and follow-up schedules to optimize treatment outcomes. [12-14] Treatment guidelines exist to guide hydroxyurea prescription, but awareness and utilization of these guidelines by SCD care providers remain uncertain.

Despite its benefits, hydroxyurea remains underutilized due to gaps in provider knowledge and variability in prescribing practices, particularly in resource-limited settings. [15-16] The maximum benefits of hydroxyurea may not be realized if physicians do not optimally prescribe it or if patient adherence is poor. [13] This study assessed the knowledge and prescription patterns of hydroxyurea among sickle cell disease care providers in Jos, Nigeria.

Materials and Methods:

Study area

The study was conducted at four tertiary healthcare facilities in Jos, Plateau State, North-Central Nigeria. These hospitals serve as referral centers for primary and secondary healthcare facilities within Plateau State and seven neighboring states, providing advanced medical care for SCD patients. According to hospital records, more than 2,500 SCD patients were receiving care at these facilities.

Study design and participants

This cross-sectional study, conducted between September and November 2018, assessed the knowledge and prescription patterns of hydroxyurea among physicians providing medical care for SCD patients in the four health facilities. SCD patients are managed by paediatricians, haematologists, family physicians, and general practitioners at these centres.

Inclusion and exclusion criteria

Physicians who provided medical care for SCD patients at the four facilities and consented to participate in the study were included. Those who had not attended to any SCD patients in the past year or who declined to provide consent were excluded.

Sample size determination

The sample size was calculated using the appropriate formula for a cross-sectional survey. [17] The parameters included the proportion of doctors with adequate prescription practices for hydroxyurea in a previous study, which was 9% (0.09), [10] the complementary probability (1 – p) of 0.91, a standard normal deviate at a 95% confidence interval (1.96), and a precision level of 0.05. After adding 5% to account for possible non-responses or incomplete responses, a minimum sample size of 132 was obtained.

Sampling method

A proportional-to-size technique was used to determine the number of doctors to include from each hospital, as previously described in a prior study. [18] Data on socio-demographics, knowledge, and prescription patterns of hydroxyurea were collected from each participant using a pretested, structured, and self-administered questionnaire.

Data analysis

Scoring and grading responses

The level of knowledge of hydroxyurea was assessed using 17 stem questions with 51 possible responses focused on general information, clinical benefits, and safety of hydroxyurea in SCD treatment. A score of one was given for each correct response, and zero for each incorrect or "I don't know" response, yielding a maximum score of 17. A percentile graph was applied to these scores, with scores above the 50th percentile (>12) classified as "adequate or good knowledge" and scores at or below the 50th percentile (≤12) classified as "inadequate or poor knowledge."

In this study, the appropriateness of prescription patterns was based on recommendations from the 2014 National Institutes of Health expert panel report and the 2018 British Society for Haematology guideline. [12, 13] For children, hydroxyurea is recommended for all children with SCA from nine months of age, regardless of clinical severity, to reduce SCD-related complications. [12, 13] In adults with SCA, hydroxyurea is recommended for those with three or more moderate-to-severe pain crises in a 12-month period, pain that interferes with daily activities or quality of life, a history of severe and/or recurrent acute chest syndrome, or severe symptomatic chronic anaemia that impacts daily life. [12, 13]

In terms of dosing, a starting dose of 10–20 mg/kg (or the nearest 500 mg for adults) was considered adequate, except for patients with chronic kidney disease, where a dose of 5–10 mg/kg is recommended. [12-13, 19] A starting dose below 10 mg/kg (or below 500 mg in adults weighing ≥50 kg) was considered underdosing. Hydroxyurea prescriptions following these recommendations were considered "appropriate," while deviations were classified as "inappropriate."

Statistical analysis

Data analysis was conducted using SPSS version 23.0 for Windows (SPSS, Chicago, IL). Descriptive statistical analysis was carried out on qualitative variables such as sex, specialty, knowledge of benefits, and safety of hydroxyurea, as well as quantitative variables such as hydroxyurea dosage. These were presented in frequency tables and expressed as frequencies and percentages. The median and interquartile range were used as a summary of indices for the maximum prescribed dose of hydroxyurea. The chi-square test was used to assess the association between respondents' demographic characteristics and

knowledge level of hydroxyurea. Pairwise comparisons with Bonferroni correction were applied to identify the specialty or cadre responsible for significant differences, holding one category as a reference per comparison. A P-value of <0.05 was considered statistically significant.

Ethical considerations

Ethical approval to conduct the study was obtained from the Health Research Ethics Committee of Jos University Teaching Hospital. Before enrolment, written informed consent was obtained from every respondent, and assurance of anonymity and confidentiality of all information supplied was also given.

Results:

A total of 132 doctors, comprising seventy-four (56.1%) males, who had been providing medical care for patients with sickle cell disease in the four tertiary hospitals, were surveyed. Family physicians made up 46.2% of the respondents, while paediatricians and haematologists accounted for 13.6% and 8.3% respectively. Approximately two-thirds of the respondents had been practicing medicine for more than six years. Only 32 (24.2%) of the doctors had ever prescribed hydroxyurea (Table 1).

Table1: Socio-demographic characteristics of the respondents

Variable	Frequency (n=132)	Percent
Sex		
Male	74	56.1
Female	58	43.9
Specialty		
Paediatrics	18	13.6
Family medicine	61	46.2
Haematology	11	8.3
General Practitioners/others	42	31.8
Cadre		
Medical officers	51	38.6
Resident doctors	52	39.4
Consultants	29	22.0
Years of practice		
1- 5years	44	33.4
6 -10 years	46	34.8
>10 years	42	31.8
Number of SCD patients seen in the last 6 months		
≤10	52	39.4
11-50	52	39.4
>50	28	21.2
Categories of patients seen		
Children only	18	13.6
Adults only	16	12.1

Both	98	74.3
Ever prescribed hydroxyurea		
Yes	32	24.2
No	100	75.8

SCD – Sickle cell disease

The majority (93.9%) of respondents had heard of hydroxyurea as a treatment for SCD, and more than half (59.1%) were aware of its availability in Jos, Nigeria. However, only 35 (26.5%) of the physicians knew about the availability of treatment guidelines for hydroxyurea use in SCD.

A total of 94 (71.2%) doctors recognized that hydroxyurea could modify the pathogenesis of SCD, while 18 (13.6%) incorrectly affirmed that hydroxyurea could cure SCD. Regarding safety, 41 (31.1%) of respondents affirmed that hydroxyurea was a drug to fear because its risks outweigh its benefits. Furthermore, 101 (78%) of participants mistakenly believed that hydroxyurea posed a significantly higher cancer risk in SCD patients than in those not exposed to it, and 78 (56.8%) incorrectly asserted that hydroxyurea causes irreversible bone marrow suppression.

The median knowledge score of hydroxyurea among participants was 12 (IQR 10–15). Overall, 65 (49.2%) participants had "adequate" knowledge, while the remaining 67 (50.8%) had "inadequate" knowledge of hydroxyurea in SCD treatment (Table 2).

Table 2: Knowledge of hydroxyurea in the treatment of sickle cell disease

Variable	**Freq (n=132)**	**Percent (%)**
Awareness of HU in SCD treatment		
Yes	124	93.9
No	8	6.1
Awareness of the availability of HU in the locality		
Yes	78	59.1
No	54	40.9
Awareness of the availability of HU treatment guideline		
Yes	35	26.5
No	97	73.5

Knowledge of HU in SCD treatment	**Correct**		**Incorrect**	
	Freq	**%**	**Freq**	**%**
General knowledge				
HU is capable of modifying SCD pathogenesis	94	71.2	38	28.8
HU is an anti-sickling agent	78	59.1	54	40.9
HU is a blood cleanser	99	75.0	33	25.0

Clinical benefits				
HU can cure sickle cell disease	114	86.4	18	13.6
HU can reduce the frequency of painful crises in SCD patients	127	96.2	5	3.8
HU can reduce the need for blood transfusion	112	84.8	20	15.2
HU can improve the quality of lives of SCD patients	128	97.0	4	3.0
Safety				
HU is a drug to be scared of	91	68.9	41	31.1
Hydroxyurea's benefits outweigh its risks	95	72.0	37	28.0
There is a well-established higher risk of cancer in SCD patients on HU than those not on HU	31	22.0	101	78.0
HU causes irreversible bone marrow suppression	57	43.2	75	56.8
Adequacy of knowledge				
Adequate	65		49.2	
Inadequate	67		50.8	

HU – Hydroxyurea, SCD – Sickle cell disease, Freq – Frequency

When stratified by specialty, 90.9% of haematologists and 77.8% of paediatricians had adequate knowledge, compared to 49.2% of family physicians and 26.2% of general practitioners ($P < 0.0001$). A pairwise comparison of specialties and knowledge of hydroxyurea using paediatrics as the reference group with Bonferroni correction showed that general practitioners had odds of adequate knowledge of 0.10 (95% CI: 0.02–0.43) compared to those in paediatrics ($P = 0.001$). For family physicians and haematologists, the odds of adequate knowledge were 0.28 (95% CI: 0.05–1.69) and 2.9 (95% CI: 0.30–28.20), respectively, compared to paediatrics ($P = 0.164$ and $P = 1.000$). Based on cadre, 69% of consultants had adequate knowledge compared to 61.5% of resident doctors and 25.5% of medical officers ($P < 0.0001$). Bonferroni correction showed that resident doctors and consultants had odds of adequate knowledge of 4.7 (95% CI: 2.1–10.2) and 6.5 (95% CI: 2.5–16.6), respectively, compared to medical officers ($P < 0.0001$ each). There was no significant association between knowledge level and sex ($P = 0.584$) or years of practice ($P = 0.203$). (Table 3)

Table 3: Relationship between characteristics of the respondents and knowledge of hydroxyurea

Variable	**Adequate knowledge n (%)**	**Inadequate knowledge n (%)**	**Total (n=132)**	**$\chi 2$**	**P value**
Sex					
Male	38(51.4)	36(48.6)	74		
Female	27(46.6)	31(53.4)	58	**0.30**	**0.584**
Specialty					
Paediatrics	14 (77.8)	4 (22.2)	18		

Family medicine	30 (49.2)	31(50.8)	61		
Haematology	10 (90.9)	1 (9.1)	11		
General Practitioners/others	11 (26.2)	31(73.8)	42	**22.43**	**<0.0001**
Cadre					
Medical officers	13(25.5)	38(74.5)	51		
Resident doctors	32 (61.5)	20(38.5)	52		
Consultants	20(69.0)	9(31.0)	29	**19.58**	**<0.0001**
Years of practice					
1-5years	17(38.6)	27(61.4)	44		
6 -10 years	24(52.2)	22(47.8)	46		
>10 years	24(57.1)	18(42.9)	42	**3.19**	**0.203**

Only 32 (24.2%) respondents had ever prescribed hydroxyurea. Of these, 26 (81.2%) initiated hydroxyurea at the recommended daily dosage of 10–20 mg/kg, while six (18.8%) underdosed their patients. The median maximum daily prescribed dosage of hydroxyurea among prescribers was 750 mg (IQR 500–1000 mg). Five (15.6%) clinicians did not exceed 200 mg, regardless of patient weight. For criteria in initiating hydroxyurea, 23 (71.9%) of prescribers followed one or more recommended criteria, while nine (28.1%) used inappropriate criteria. Seven (21.9%) physicians based their prescriptions on established treatment guidelines, while 25 (78.1%) did not refer to any guidelines. Regarding the dosing regimen, the seven physicians (21.9%) who followed guidelines used an escalated dosing regimen while the other 25 (78.1%) administered hydroxyurea at fixed dosages. All seven providers who used treatment guidelines reported being "very comfortable" with prescribing hydroxyurea, while five (15.6%) of prescribers reported discomfort with its use (Table 4).

Table 4: Prescription pattern among prescribers of hydroxyurea

Variable	Frequency n=32	Percent
Appropriateness of criteria for initiating hydroxyurea		
Appropriate	23	71.9
Inappropriate	9	28.1
Starting dose of hydroxyurea		
<10mg/kg	6	18.8
10 -20mg/kg	26	81.2
Maximum dosage of hydroxyurea prescribed(mg)*		
<500	5	15.6

500 - <1000	13	40.6
≥ 1000	14	43.8
Prescription based on established guideline		
Yes	7	21.9
No	25	78.1
Dosage regimen		
Fixed	25	78.1
Escalated	7	21.9
How comfortable prescribing HU		
Very comfortable	7	21.9
Comfortable	20	62.5
Not comfortable	5	15.6

* Maximum dosage of hydroxyurea (mg) providers would not want to exceed in their practice
HU - hydroxyurea

Discussion:

This study highlights the level of knowledge and prescription practices regarding hydroxyurea among physicians caring for patients with sickle cell disease. Addressing gaps in knowledge and prescribing patterns can help remove barriers to hydroxyurea use, ensure its appropriate administration, and maximize its benefits for patients.

The participants in our survey exhibited a high level of awareness regarding the role of hydroxyurea in the treatment of sickle cell disease, with the majority having information on its use for therapy. Similar high awareness was documented in research conducted in the United States among physicians treating adult patients with sickle cell disease [20]. The increased awareness of hydroxyurea in these studies was anticipated, as the participants were physicians who had gained knowledge in multiple medical disciplines, including haematology, through their medical education and ongoing professional development. However, specific knowledge about the pharmacological properties of hydroxyurea, including its classification, clinical benefits, and safety profile was lacking. Only approximately half of the respondents possessed adequate knowledge in these areas.

One possible explanation for this knowledge gap is the limited use and exposure to hydroxyurea among physicians, particularly in settings where the drug is not widely prescribed. This aligns with findings from a recent study that highlighted knowledge deficits as a significant barrier to the effective use of hydroxyurea in low-income settings [16]. In other words, a lack of familiarity with the drug not only results from its underutilization but also contributes to its continued limited use, creating a cycle of poor awareness and low prescription rates.

Our study also revealed disparities in various aspects of hydroxyurea knowledge. While the majority of respondents were aware of its clinical benefits, a significant number had limited knowledge of its safety profile. For instance, over half incorrectly asserted that hydroxyurea causes irreversible bone marrow suppression, despite evidence that such suppression is reversible and dose-dependent [9, 21]. Additionally, around 80% of participants assumed an increased cancer risk for SCD patients on

hydroxyurea, a misconception that is not evidence-based. Recent studies have demonstrated compelling evidence that hydroxyurea in the treatment of patients with sickle cell disease carries no increased risk of carcinogenicity [22, 23]. This inadequate knowledge of hydroxyurea's safety could hinder its use and likely contributed to the low prescription rate observed. Hydroxyurea has some known side effects such as reversible bone marrow suppression, skin hyperpigmentation, and gastrointestinal disturbances [9, 12]. Other potential adverse events such as leg ulcers and reproductive effects have low-quality evidence of causality with hydroxyurea therapy [12]. Consequently, facts about hydroxyurea that are devoid of false and unproven assertions need to be communicated to patients by care providers to facilitate informed decision-making.

This study also established that the knowledge of hydroxyurea varied by specialty and experience. The proportion of SCD care providers with adequate knowledge was highest among haematologists, followed by paediatricians while the general practitioners had the least knowledge about hydroxyurea. This disparity may relate to differences in the quality and level of training on sickle cell disease care received by these practitioners, the number of SCD patients they manage, and the level of expertise in the care of the patients. In developed countries, similar studies found high hydroxyurea knowledge levels among physicians, likely due to additional training in haematology [20, 24]. Nevertheless, with a very huge burden of SCD in Nigeria, coupled with the fact that the country has few haematology specialists, non-haematologists will be required to meet the needs of these numerous patients. Additionally, integrating sickle cell disease management into primary healthcare systems linked to district-level (General) hospitals, as recommended by Odame [5], could improve care delivery and make treatments like hydroxyurea accessible to a larger population. Therefore, it is essential to provide these physicians with training on the effective and safe use of hydroxyurea, as well as other aspects of SCD care, within the context of local practice.

Less than a quarter of SCD care providers in our study prescribed hydroxyurea, a finding similar to reports of some previous studies [20, 24]. Over a quarter of the prescribers of hydroxyurea in this study did not initiate hydroxyurea in accordance with the current recommended criteria thus indicating medical drift and inappropriate prescription of hydroxyurea [12, 13, 19]. Similar inappropriate use of hydroxyurea was documented in a study from a central hospital in Saudi Arabia where 10% of the patients who received hydroxyurea did not have the recommended indications for hydroxyurea therapy [25].

Among the few prescribers in our study, a significant number administered hydroxyurea at lower-than-recommended doses, primarily due to concerns about potential side effects. This practice may result in a suboptimal clinical response, which, in turn, could discourage patients from continuing hydroxyurea treatment or adhering to their prescribed regimen, ultimately leading to poorer health outcomes. A study by Creary et al had documented reports of patients who decided to discontinue hydroxyurea on account of poor clinical response that was partly due to suboptimal use of hydroxyurea [26].

The fixed-dose regimen was favoured by 78.1% of respondents, while 21.9% preferred dose escalation. This preference aligns with findings by Inusa et al., where only 28% of participants, spanning Europe and Africa, used an escalated dosage regimen [27]. The fixed dosage schedule was more popular because it was less cumbersome as it neither requires any dosage adjustment nor frequent treatment monitoring, unlike the escalated dosage regimen. Interest in fixed dosing is growing in low- and middle-income countries for its cost-effectiveness and lower monitoring requirements [27, 28]. Incorporating strategies to improve adherence and reduce monitoring burdens could make hydroxyurea therapy more feasible in resource-limited settings. Fixed-dose regimens, which have shown promise in improving access while ensuring cost-effectiveness, align with current efforts to optimize treatment in low-resource settings [5]. However, further studies are needed to compare the benefits and disadvantages of escalated versus fixed-dosage regimens in SCD therapy in LMICs.

Furthermore, all respondents who prescribed hydroxyurea following established guidelines reported feeling "very comfortable" with prescribing it, while those who were "not comfortable" did not use guidelines. The use of treatment guidelines perhaps boosted their confidence in the prescription of hydroxyurea. The National Heart, Lung, and Blood Institute expert panel strongly recommended the use of an established prescribing and monitoring protocol to ensure proper use of hydroxyurea and maximize benefits and safety [12].

The multi-level standards of care (SoC) guidelines for sickle cell disease, developed by the Sickle Pan-African Research Consortium (SPARCo), serve as an essential tool for harmonizing hydroxyurea treatment across sub-Saharan Africa. [29] These guidelines provide structured recommendations to ensure consistency in treatment approaches, improve patient outcomes, and facilitate the broader adoption of hydroxyurea in resource-limited settings [29]. However, the mere existence of treatment guidelines does not guarantee awareness or adoption by healthcare providers, as observed in this study. Targeted efforts are needed to enhance awareness, promote advocacy, and encourage the integration of these guidelines into clinical practice.

The effect of the suboptimal prescription of hydroxyurea by the care providers in our study on the clinical outcomes of the patients was not assessed since it was not within the scope of the study. Assessing this could have provided more information. Another limitation of this study is that being a cross-sectional survey, recall bias cannot be completely ruled out.

In conclusion, this study demonstrates a high prevalence of inadequate knowledge of the clinical benefits and safety of hydroxyurea, and inconsistent hydroxyurea prescribing practices among SCD care providers in this setting. Therefore, training on the effective and safe use of hydroxyurea is imperative, and adopting evidence-based treatment guidelines may help standardize prescription practices.

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