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Hydroxyurea Uptake among Children with Sickle Cell Anaemia at a Tertiary Hospital in Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Sickle cell anaemia (SCA) is the most common genetic disease in the world, with Sub-Saharan Africa bearing the heaviest burden. Despite the availability and known benefits of hydroxyurea, its use in low- and middle-income countries has been limited. The purpose of this study was to determine the proportion of children with SCA who receive HU at Rivers State University Teaching Hospital (RSUTH)'s paediatric haematology clinic, as well as to highlight the sociodemographic correlates of users.

A descriptive cross-sectional study was done at the Paediatric Haematology clinic of RSUTH. The study participants were children with SCA attending the clinic. An interviewer administered semi-structured questionnaire was used to obtain socio-demographic data and information concerning the uptake of HU from caregivers of the subjects.

This study enlisted the participation of 88 children. There were 38 (43.2%) males and 50 (56.8%) females, for a male to female ratio of 1:1.3. The subjects' ages ranged from 2 to 18 years. Approximately half of the study participants came from affluent families. In total, 26 (29.5 percent) of the study participants used hydroxyurea. The use of hydroxyurea was significantly higher in the upper socioeconomic class compared to the middle and lower classes. Its use was also significantly higher among those suffering from sickle cell disease complications.

Hydroxyurea uptake remains low. Some of the factors to consider when attempting to increase Hydroxyurea uptake should be affordability and advocacy, taking into account the socioeconomic status relationship between users and uptake.

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1. INTRODUCTION

Sickle cell disease (SCD) was the first genetic disease to be described as molecular over six decades ago [1]. It encompasses a group of genetic disorders of haemoglobin synthesis that occurs following the inheritance of a sickle (HbS) gene from one parent and another abnormal b-globin gene, from the other parent [2]. Over the past decades a lot of effort has gone into research to better understand the pathophysiological basis of the disease as well as identify key areas for pharmacological intervention. The discovery of hydroxyurea (HU) as a disease-modifying drug has made tremendous impact in improving the quality of life of people living with SCD [3]. In the pre-hydroxyurea era, research showed that about 50% of SCD patients in sub-Saharan Africa die by 5 years of age [4]. The use of hydroxyurea, in addition to other medical interventions like new-born screening, penicillin prophylaxis, pneumococcal vaccinations, and stroke prevention strategies, has improved the overall health and life expectancy of people living with sickle cell disease over the last decade [5].

Hydroxyurea (or Hydroxycarbamide) acts by increasing Hb F (Haemoglobin F) production with a resultant decrease in the relative concentration of Hb S (Haemoglobin S). The presence of Hb F then interferes with polymer formation and increases the duration of the delay between hypoxia and polymer formation [6]. This ultimately leads to less haemoglobin polymerization and precipitation, manifesting clinically as a remarkable reduction in the episodes of vaso-occlusive crisis, hospitalizations, need for blood transfusions and acute chest syndrome [7,8]. On the flip side, because of its suppressing effect on the bone marrow, the blood cell lines will need to be monitored periodically to ensure that bone marrow toxicity is avoided. With close follow up, dose adjustment and laboratory support a maximum tolerable dose is targeted for each patient to achieve the optimal benefits of HU [9-11]. Overall, HU is available, relatively affordable and has ease of administration as an oral daily dose. It has also been in use for cancer treatment for over 40 years [6].

Despite its established beneficial effects, the uptake and utilization of HU has been poor especially in sub- Saharan Africa where the disease burden is highest [12]. Effectiveness studies have identified patient, provider and system level barriers to uptake of HU in Lower- and middle-income countries [13,14]. These barriers range from the lack of expertise of the medical practitioners and their uncertainty in prescribing and monitoring their sickle cell patients on HU, to the unavailability and unaffordability of the medication to the patients and their families [15]. Another barrier reported is the health belief, awareness, and acceptance of the medication as well as fear of side effects of therapy among the patient families [15-17]. The paucity of and regional differences in treatment guidelines is also a significant stumbling block in HU uptake [14,18].

This study, therefore, set out to determine the uptake/prevalence of HU use among a cohort of 88 sickle cell anaemia patients on follow up at a tertiary health facility as well as to assess the sociodemographic correlates of users. Information from this study will be useful in further advocacy to improve HU uptake in our locality.

2. METHODOLOGY

The study was carried out at the Rivers State University Teaching Hospital (RSUTH), formerly known as Braithwaite Memorial Specialist Hospital, a state government-owned tertiary hospital in the heart of Rivers State. It is a 365 - bed hospital that serves indigenes of Rivers state as well all those of neighbouring states in the south-south and south-east Nigeria [19]. A descriptive cross-sectional study was done at the Paediatric Haem-oncology out-patient clinic of RSUTH over a period of 5 months (November 2020 to March 2021). The study participants were children with Sickle Cell anaemia, 18 years and below attending the paediatric haem-oncology clinic.

The paediatric haem-oncology clinic is a weekly clinic that runs from 8 am to 4 pm every Wednesday. Patients who had started attending the clinic within the preceding 3 months were excluded. The details of the study and the information required were explained to caregivers. They were also made to know that their participation in the study is entirely voluntary and non-participation will not attract any penalties. The study included all patients with sickle cell anaemia (Hb SS, Hb SC) in steady state attending the haem-oncology clinic. An interviewer-administered semi-structured

questionnaire, designed by the researchers, was used to obtain socio-demographic data and information concerning the uptake of hydroxyurea from caregivers of the subjects. The socio-economic class was calculated using the Oyedeji classification [20] which has been standardized for use on the Nigerian population. The Oyedeji classification uses the educational level and occupation of the parents to determine the social class of the family. Information on the uses, benefits and possible side effects of HU was given to all study participants. Data were cleaned and analysed using SPSS version 22.

3. RESULTS

A total of 88 children participated in this study. There were 38 (43.2%) males and 50 (56.8%) females with a male to female ratio of 1: 1.3. The ages of the subjects ranged from 2 to 18 years (Table 1). About half of the study participants were of high socioeconomic class (Table 2). Most subjects were from the South-south/South-East geopolitical zones of Nigeria.

Overall, hydroxyurea was being used by 26 (29.5%) of the study participants (Fig. 1).

There was no significant association between the use of hydroxyurea and age or sex. Hydroxyurea use was significantly higher among the high socio-economic class, compared with the mid and low class. Its use was also significantly higher among those with sickle cell complications (Table 3).

Table 1. Age distribution of respondents

Age (in years)	Frequency (n)	Percentage (%)
Under 5	16	18.2
6-10	36	40.9
11-15	32	36.4
16-20	4	4.5

Table 2. Socio economic class of respondents

Socio-economic class	Frequency (n)	Percentage (%)
High	46	52.3
Middle	35	39.8
Low	7	7.9

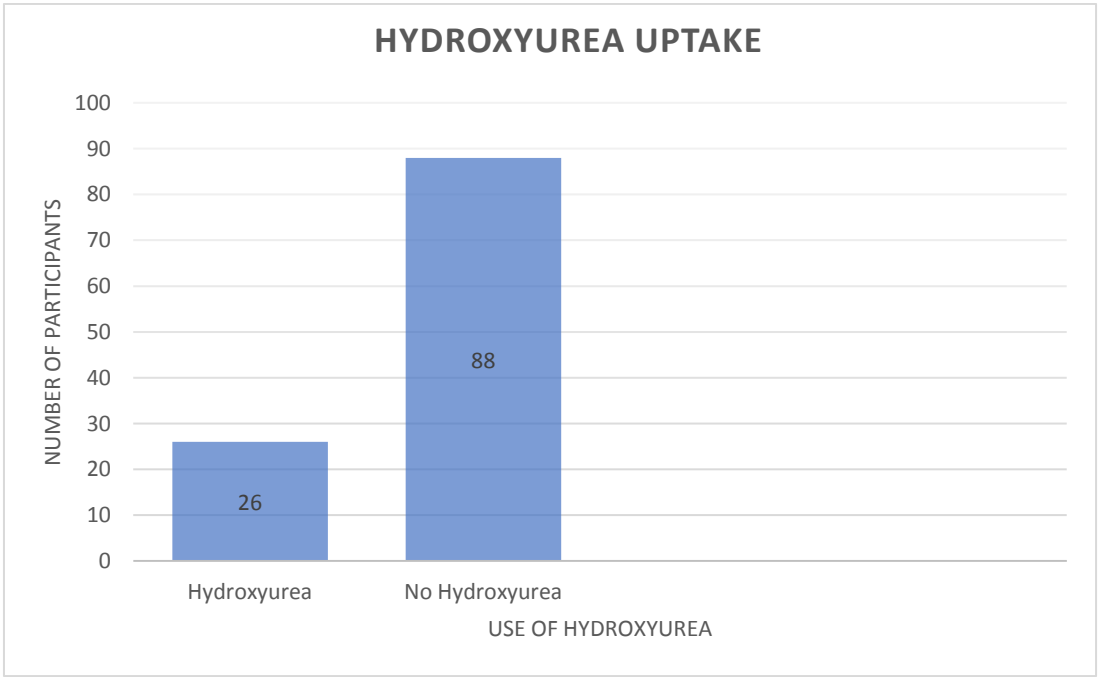

Fig. 1. Showing uptake of Hydroxyurea among study participants

Table 3. Association between Socio-demographic Factors and Hydroxyurea use among the Study Subjects

Variables	Hydroxyurea use		Total n (%)	x^2	p-value
	Yes n (%)	No n (%)			
Age group (in years)					
Under 5	2 (12.5)	14 (87.5)	16 (100.0)	6.325	0.968
6-10	14 (36.8)	24 (63.2)	38 (100.0)		
11-15	10 (31.2)	22 (68.8)	32 (100.0)		
16-20	0 (0.0)	2 (100.0)	2 (100.0)		
Gender					
Male	14 (28.0)	36 (72.0)	50 (100.0)	0.002	0.784
Female	12 (31.5)	26 (68.4)	38 (100.0)		
Social class					
High	16 (34.8)	30 (65.2)	46 (100.0)	0.367	0.003*
Middle	10 (28.5)	25 (71.5)	35 (100.0)		
Low	0 (81.2)	7 (100.0)	7 (100.0)		
Sickle cell complications					
Present	15 (71.4)	6 (28.6)	21 (100.0)	21.863	0.000*
Absent	11(16.4)	56 (83.6)	67 (100.0)		

**Statistically significant*

4. DISCUSSION

The beneficial effect of Hydroxyurea has been described in many studies in sub-Saharan Africa, yet its uptake remains low [21]. Less than a third of the respondents in this study were receiving hydroxyurea at the time of the study. The finding in this study is consistent with the reports of other researchers in Nigeria and Jamaica who showed a prevalence of HU use of between 20 to 40% of the population of sickle cell patients studied [13,14,16,22]. In contrast to the low rate of hydroxyurea uptake observed in this study, a recent study conducted among children aged 1-10 years from four Sub-Saharan countries (Angola, Congo, Kenya, Uganda) recorded a remarkably high uptake and adherence rate of nearly 95% in over three years [12]. However, this high rate could be attributed to an independent party who generously donated the drugs used throughout the study, emphasizing the negative impact of cost and economic factors on hydroxyurea use in resource-limited countries.

In the past couple of years, a major reason for the low uptake of HU was its relative unavailability in local pharmacies [21]. This scarcity also resulted in the sale of HU at a considerably high price. Global efforts to address the sickle cell disease burden in low- and middle-income countries were successful in encouraging the local production of the medication by Bond Chemical industries in Nigeria going by the brand name Oxyurea. The Brand Oxyurea is effective and a pack of thirty 500 mg capsules cost N1313 (which is presently about 3 dollars) [21].

Furthermore, while the issue of drug availability is being addressed, other notable barriers to the uptake of hydroxyurea have been identified. An interesting finding of this study was that following statistical analysis of the data gathered; the use of HU was significantly higher among the high socio-economic class. Other socio-demographic factors like age and sex did not have any significant relationship with HU use. The National Bureau of Statistics estimated in 2019 that 4 out of 10 Nigerians lived below the poverty level of 1 dollar per day, and while this body predicted that this figure will rise by 5% by 2022, the emergence of COVID-19 has tipped the scales even farther to the right [23,24]. Furthermore, due to the low coverage of health insurance, healthcare expenditures are regrettably covered primarily by out-of-pocket payments in Nigeria [25,26]. The combined effect of these shortfalls is evident in this study, which demonstrated that of all the variables examined, socioeconomic status emerged as the most prevalent predictor related to considerable hydroxyurea use. Hence a major stride to improve the uptake of hydroxyurea will be by exploring was to make the medication more affordable to the sickle cell population.

Interestingly, in this present study, hydroxyurea use was significantly higher amongst the

respondents who had health complications attributable to sickle cell disease. This, in some sort, highlights the acceptance of HU among parents when a life-changing or debilitating complication of sickle cell disease has occurred. The 'fire-brigade' approach to the management of sickle cell anaemia is no longer regarded as good clinical practise. The current goal of management of sickle cell disease is to, as much as possible, anticipate and prevent complications from occurring ab initio.

Other barriers to the uptake of hydroxyurea include the lack of a national treatment guideline on hydroxyurea, a wide knowledge gap among health care providers on the effectiveness and safety profile of hydroxyurea, the relative scarcity of hydroxyurea and uncertainty about its risks due to poor monitoring of blood indices [15,16,21]. Hydroxyurea has an excellent safety profile, as evidenced by robust studies across the world [3,5,12,27-30]. A recent multi-centre research in Africa found that a daily dose of about 20mg per kilogram of hydroxyurea had no notable adverse effects [12]. Although the safety concerns of hydroxyurea were not explored in this study as a potential barrier, it is quite evident that the benefits outweigh its risk. As a result, all health care practitioners should include hydroxyurea in the routine management protocol of sickle cell anaemia in both adults and children.

Addressing the barriers in the uptake of HU in Nigeria, which has the world's largest population of people living with sickle cell anaemia, must include the use of a well-designed local treatment guideline that is adapted for use in this environment [31,32]. Standard guidelines should emphasize a safe daily dose regimen, feasible periodicity of follow up and laboratory monitoring to make HU therapy consistent and efficient. The guideline should also encompass strategies to improve the knowledge of health care professionals on the benefits of hydroxyurea in the management of sickle cell disease, its safety profile as well as toxicity indicators. To ensure that hydroxyurea is made accessible to affected individuals, the government and other concerned parties should facilitate measures to ensure that the drug is widely available preferably at a reduced cost. The establishment of adequate clinical and laboratory infrastructure is critical for the timely detection and surveillance of sickle cell disease as well as the monitoring and evaluation of any hydroxyurea-related side effects. Finally, indigenous researchers should be funded to conduct robust clinical studies that will investigate any additional socio-cultural or religious factors that may preclude the intake of hydroxyurea. These studies should also aim to evaluate any other unreported side effects of hydroxyurea as well as investigate the impact of the drug on locally endemic diseases.

5. CONCLUSION

The uptake of hydroxyurea is still poor. Some of the factors to be considered while making effort to improve Hydroxyurea uptake should be affordability and advocacy considering the socio-economic status relationship of users and uptake.

6. RECOMMENDATIONS

Efforts to address the affordability barrier to use of HU may improve HU uptake among sickle cell patients in Nigeria. HU may be included as medications provided under the National health insurance scheme. The cost of the periodic laboratory investigations recommended for patient monitoring during use of HU should also be subsidized or completely waived if possible. Continuous education should be given to sickle cell patients, their caregivers and the general public on sickle cell disease, its management and the beneficial role of hydroxyurea.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

All patients who met the selection criteria and who gave informed written consent were recruited into the study. All procedures in this study were conducted in accordance with the Rivers State University Teaching Hospital Ethics Committee approved protocols. Ethical approval was obtained from RSUTH Ethics Committee (RSUTH/REC/2021132).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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