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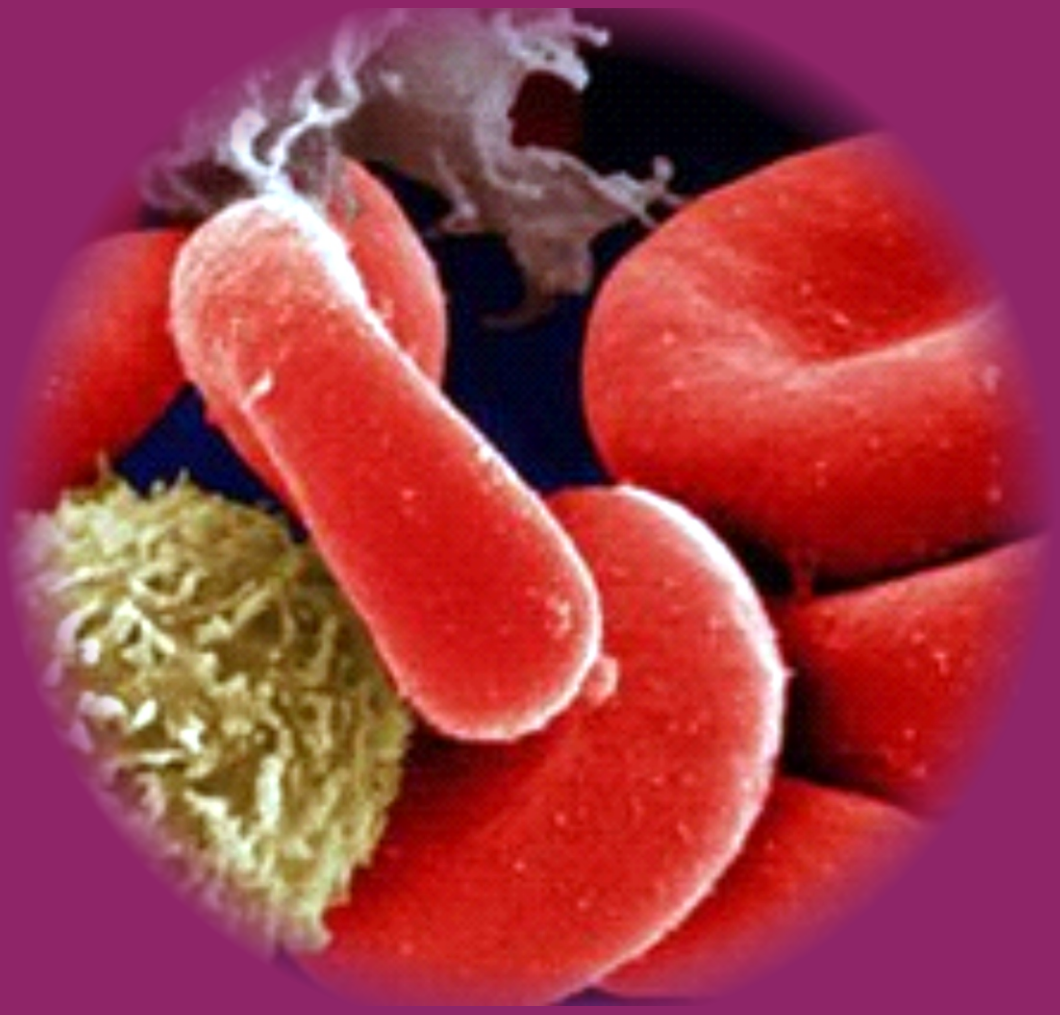

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ORIGINAL RESEARCH ARTICLE

Knowledge and Utilisation of Hydroxyurea among Patients with Sickle Cell Disease in Zaria, Nigeria: A Comparative Study

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ABSTRACT

Background:

Hydroxyurea (HU), an antimetabolite, was introduced in 1998 in USA as a routine medication for severe SCA, but it is yet to be accepted for routine care in our centre.

Aims and Objectives:
This study determined the knowledge and utilisation of HU among patients with SCA in Zaria.

Materials and Methods:
Bio-data, socio-demographic characteristics, Haematological parameters, knowledge and use of HU were assessed using questionnaires in 2006 and 2016 respectively. Data were analysed using SPSS version 20 with level of significance at $p \leqslant 0.05$.

Results:
A total of 208 (male 50% vs female 50%) and 119 (male 42% vs female 58%) patients with SCA in 2006 and 2016 respectively were interviewed. The mean ages were 22.0±7.0 vs 23.0±5.0 respectively (p=0.237), Frequency of crises per year was 6.1±2.3 vs 5.6±3.1 (p=0.098), blood units transfused per annum was 3.0 ±1.5 vs 2.3±1.1 ($p < 0.0001$) in 2006 and 2016 respectively. Four (1.9%) of 208 and 24 (20%) of 119 patients with SCA were aware of HU as a medication while none 0/208 (0%) vs 18/119 (2.6%) were on HU therapy. Barriers to the use of HU were cost of medication 98% vs 82%, non-availability 95% vs 98%, increased follow up visit 98% vs 88% and drug restriction 98% vs 91% in 2006 and 2016 respectively.

Conclusion:
Knowledge and utilisation of HU are increasing in Zaria, perceived barriers to its use did not change over the ten year study period. Thus continuous patient education on the advantages of HU therapy in SCA is recommended to increase utilisation.

Keywords: sickle cell anaemia, Hydroxyurea, utilisation

INTRODUCTION

The global burden of sickle cell disease (SCD) is significant. Each year about 400,000 infant are born with a major haemoglobin disorders – including more than 200,000 cases of SCD in Africa, 150,000 in Nigeria alone. [1,2] Sickle-Cell Anaemia (SCA) contributes the equivalent of 5% of under-five mortality rates on the African continent, more than 9% of such deaths in West Africa, and these add up to 16% of under-five deaths in individual West African countries. [1,2] Millions of people are estimated to be living with SCD in Nigeria. [1,2] Life expectancy among patients with SCA remains low in addition to life long suffering with chronic pain, severe anaemia and chronic organ damage. [2-4]

Hydroxyurea (HU) is the most successful therapy for homozygous sickle cell diseases. [2] Hydroxyurea is an anti-metabolite cytotoxic agent that inhibits DNA synthesis by inhibiting ribonucleotide reductase enzyme. [5,6] The clinical efficacy of HU in SCD follows its broad pharmacologic effects including increasing haemoglobin F levels in red blood cells, preventing the formation of haemoglobin S polymers, dose-related cyto-reductive effects on neutrophils, increasing the water content of RBCs, increasing deformability and successful micro-vascular navigation of sickled cells, and

altering the adhesion of RBCs to endothelium by down regulating the expression of adhesion molecules. [5,6] Treatment with HU is associated with significant decrease in the yearly rate of painful crises, hospitalizations, incidence of chest syndrome, priapism, hepatic sequestration, and blood transfusion requirements by up to 50% and mortality reduction by 40%. [7] HU has also been advocated to be a valid alternative to chronic transfusion regimen in patients with SCD and stroke. [8,9] Studies of HU in children have shown similar efficacy as adults. [10-12] Various studies have confirmed the benefits of HU, even in children $\leqslant$ 2 years of age, and its possible role in primary stroke prevention. [11,12] Early administration of HU may therefore decrease long term organ complications associated with SCD. It has been observed that delaying the age at which HU is instituted is associated with increased mortality.

HU is underutilised in SCD management in the United States despite adequate efficacy, cost effectiveness and long term management experience. [12] Hospitalization rates and cost of care for adults with SCD in the state of Maryland, USA was reported to have (paradoxically) increased significantly since approval of HU and about 70% of patients who are appropriate candidates for HU may not be taking the medication. [12]

Reasons for the poor utilizations rates may be related to lack of experience of HU by non-haematologists and toxicity concerns by patients and some physicians. [13] There are only a few reports on the utilization of HU in SCD especially from Africa, a part of the world with the highest burden of the disease. [14] The criteria for HU use according to the Nigerian national guideline for the control and management of sickle cell include; $\geqslant$ 5 crises, 3-4 crises per year and either neutrophil count of $\geqslant 10 \times 10^9$/L, or platelet count $\geqslant 500 \times 10^9$/L, abnormal TCD > 200cm/s, Acute chest syndrome and Stroke. [15] This study was to determine the utilization of HU by patients with SCD in a tertiary institution in North-West, Nigeria.

MATERIALS AND METHODS

This was a cross-sectional comparative study of knowledge and utilisation of HU among patients with SCD in Ahmadu Bello University Teaching Hospital (ABUTH), Zaria. Ethical approval was sort from the Ethical Committee of ABUTH Zaria, before conducting both studies. Consenting patients with SCD (HbSS/HbSC), aged $\geqslant$15 years in steady state; "*a point in time when the patient is not experiencing an acute painful crisis or any change due to therapy".* [16] Patients attending the Haematology Outpatient Clinic of ABUTH were interviewed in 2006 and in 2016 and their responses were analysed. The questionnaire determined bio-data, socio-demographic parameters and Knowledge, utilisation and barriers to HU use were determined. Data obtained were analysed by SPSS version 20 using range, mean and standard deviation with level of significance set at p-value of $\leqslant$ 0.05.

RESULTS

There were no significant differences in the socio-demographic and clinical variables of the patients seen in 2006 and 2016 (Table1). The age range of the participants was 15-28 years. There was no patient on HU therapy in 2006 and only 4(1.9%) of them were aware of HU as a treatment option for SCD. Thirty (30) percent of patients were identified as potential candidates for HU therapy based on clinical and haematological criteria in 2006. The major barriers to HU utilisation identified in 2006 and 2016 were cost of medication, drug availability, frequent follow up visits &drug restriction (Figure 1).

Table 1: Clinical Parameters in HU naïve patients with SCD U in Zaria, Nigeria

	2006 Total = 208	2016 Total = 119	
Clinical Parameters	**Mean ±SD**	**Mean ±SD**	**P-Value**
Age (years)	22.0 ±7.0	23.0 ±5.0	0.237
Freq. of Crisis/year	6.1 ±2.3	5.6 ±3.1	0.098
Freq. of Transfusion/year	3.0 ±1.5	2.3 ±1.1	<0.0001*
Key: SD= standard deviation, MEDCALC (Crisis and Transfusion)			

Table 2: Awareness, utilisation and sources of information about HU among patients with SCD in Zaria, Nigeria

	2006 Total = 208	2016 Total = 119
	N (%)	**N (%)**
Awareness of HU	4(1.9)	24(20.2)
Sources of Information	Physicians	Physician/internet/media
No of patients on HU	0 (0%)	18(6.6%)

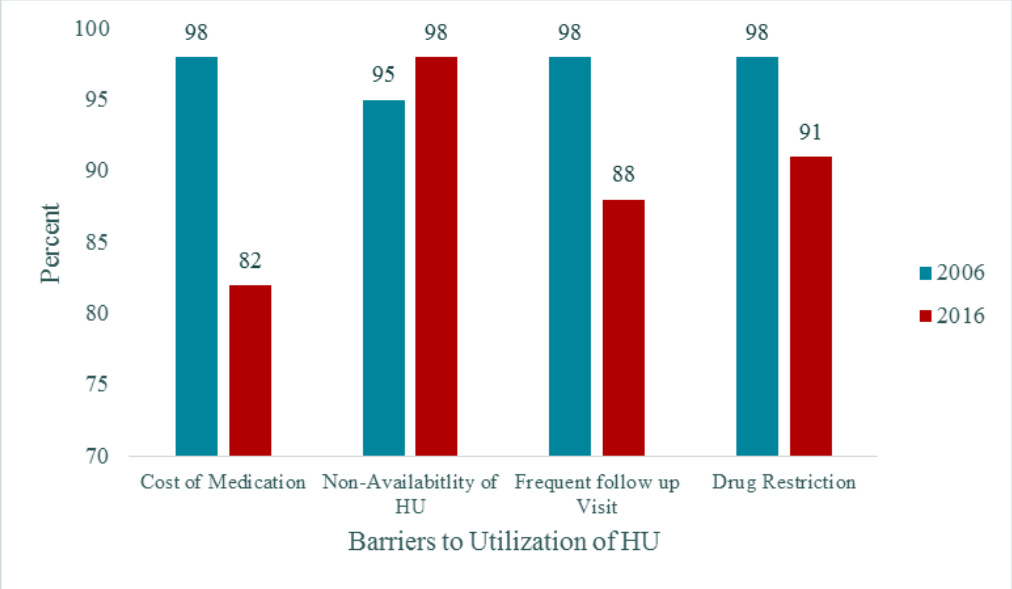

Figure 1: Barriers to Utilisation of HU among patients with SCD in Zaria, Nigeria

DISCUSSION

The use of HU for the treatment of SCD requires significant and long term commitment by patients, family members, physicians and the health care system. The first step towards utilising any drug is awareness. All the patients got information from their physicians. In 2006, the low awareness and knowledge (1.9%) of the use of HU among these patients increased remarkably to 20% in 2016. Similarly the source of information of HU which was obtained in 2006 only from the physicians (100%) improved to varied sources of information ranging from physicians, internet, social media and a combination of these in 2016. This remarkable increase may be due to access to information via the internet.

Barriers to HU utilisation identified by doctors in Nigeria include safety and toxicity concerns. [17] This may be especially important in an environment where, effective follow up of patients, logistic and communication remain a challenge. Additionally, the educational level of patients may not be sufficient enough to allow them a thorough appreciation of the potential complications of the drug and the absolute need for close monitoring of blood counts. Specific safety concerns among doctors identified in other studies include the potential for HU-related reactivation of latent tuberculosis, carcinogenesis and teratogenicity. [18]

Rare cases of leukaemia related to HU use have been reported. [19] Hydroxyurea crosses the placenta and is embyrotoxic in animal models (Pregnancy Category D). [20] Although there are no adequate human studies on teratogenic effect of HU in our environment, most physicians offer contraceptive use to patients on HU to prevent pregnancy. Several case reports suggest that HU may have minimal teratogenic effect on the developing human foetus, thus the risks ascribed to HU exposure during pregnancy may have been overestimated. [20] Further studies with larger numbers of patients receiving HU during pregnancy, with longer follow-up of exposed children and more careful assessment of teratogenic effects, are required. The socio-cultural environment of Nigeria and the special priority placed on childbirth is a major concern for the use of HU as indicated by the almost universal concern expressed by patients. [20-22] Additional, HU is excreted in human milk and not recommended while breastfeeding thus placing an additional challenge in the postpartum period in an environment like Nigeria where breast feeding is strongly encouraged and preferred. [21,22] In the USA, peri-contraception management of patients with SCD has generally included withholding HU before and during pregnancy and breast feeding period and switching to transfusions program for the required duration as necessary. The duration of breast feeding is on the average much longer in developing countries and this would indicate the potential for a prolonged interruption of treatment with HU in such settings. [21,22]

The use of HU requires close monitoring with twice weekly blood counts for evidence of bone marrow suppression until a stable or maximally tolerated dose is obtained before switching to monthly blood counts. This has increased cost, compliance and life style implications. These concerns were expressed by patients in Nigeria. Additional, concerns identified by physicians include patient compliance, drug availability and affordability. While HU causes macrocytosis that can easily be used for compliance monitoring while response to HU can be assessed using clinical and haematological criteria. Physicians in Africa often refer to the lack of high performance liquid chromatography (HPLC) machine for quantifying foetal haemoglobin (Hb F) as a barrier to instituting HU therapy. This is clearly not a reason for withholding therapy as several centers in the USA do not routinely check Hb F levels as a marker to response to HU. Hydroxyurea therapy may mask the development of folate deficiency, a situation common in SCD due to rapid red cell turn over and especially concerning in developing countries prone to folate deficiency. All patients with SCD should receive folate supplementation. [3]

CONCLUSION

Our findings indicate that there is a poor awareness and utilisation of HU among patients with SCD in ABUTH Zaria. Due to ignorance about the drug, non-availability, high cost and the need for increase in follow up visits. Therefore we recommend continuous physician and patients' education on the safety and efficacy of HU in SCD management. This will enhance the utilisation and ultimately the quality of life among patients with SCD in Zaria.

Authors' Contribution:

Authors contributed to the study design, data collection and manuscript preparation.

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Conflict of Interest:

None.

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/2. Cytogenetics with FISH, CISH.

/3. Haematopathology – diagnosis of Lymphomas.

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Deadline for abstract submission 12.00 pm June 30 2018

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