Hydroxyurea therapy in adult Nigerian sickle cell disease: a monocentric survey on pattern of use, clinical effects and patient's compliance.

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Abstract

Background: The clinical prospects of hydroxyurea therapy in the management of sickle cell disease (SCD) require evaluation in the Nigerian setting to develop indigenous guidelines. This survey examines the pattern of hydroxyurea therapy, its clinico-haematologic benefits and safety profile in Nigerian SCD subjects.

Methods: A cross sectional pilot survey was carried out among 60 adult SCD subjects over 3 months. Data on clinical phenotypes, relevant haematological parameters and details of hydroxyurea therapy were obtained using a structured questionnaire through an interview process and case file review.

Results: The median age was 30 years. Thirty-four (56.7%) of the subjects are aware of hydroxyurea therapy in SCD. Twenty-four (40%) SCD patients had previously used hydroxyurea. Only 4 subjects were fully compliant. Reasons for non-compliance included poor knowledge and lack of funds. In particular, hydroxyurea reduced leucocyte count and increased mean red cell volume (MCV) in compliant subjects.

Conclusion: Hydroxyurea use is low among Nigerian SCD subjects despite its proven efficacy/clinical prospects in the developed nations. Large scale multicenter studies and clinical trials are needed to form a basis for developing standard local treatment protocol for its use.

Keywords: Hydroxyurea therapy, Nigerian sickle cell disease, pattern of use, clinical effects, patient's compliance.

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Introduction

Sickle cell disease (SCD) remains a major public health challenge, affecting over 3 million Nigerians[1,2]. Estimates put SCD prevalence between 2 and 3%, in a population of 170 million Nigerians[2-4]. Low levels of awareness/knowledge, poor case finding strategies and sub-optimal treatment continue to fuel morbidity and mortality rates in the country[5-9]. The introduction of novel agents such as hydroxyurea has greatly impacted on disease outcome in developed climes such as US[10-13]. There are indications that hydroxyurea is under utilized in the Nigerian setting[14,15].

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Recent studies suggest that Nigerian SCD is still associated with significant pain burden and other morbidities, which might be reduced through appropriate interventions such as hydroxyurea[9,14,16-18]. Giving the constant risk of exposure to precipitants such as malaria and other infections, there is a palpable need to critically evaluate, standardize, advocate and monitor interventional therapies such as chronic transfusions, hydroxyurea and haemopoietic stem cell transplant in the Nigerian setting. Data on the level of hydroxyurea awareness, pattern of use and benefits is needed.

Since its approval by FDA in 1998 for treatment of moderate to severe sickle cell disease, hydroxyurea (otherwise called hydroxycarbamide) has shown immense benefits in ameliorating SCD[19-21]. Hydroxyurea modifies the com-

plex pathophysiology of SCD through multiple mechanisms including induction of fetal haemoglobin production, improving cellular hydration, marrow suppression (reduction of leucocyte and platelet counts), anti-adhesive properties and production of nitric oxide (vasodilator)[19,22]. Clinically, this translates to reduced frequency and intensity of bone pain crisis, hospitalizations, blood transfusions, thus better quality of life[20,23,24].

This study evaluates the level of awareness, drug use pattern, clinic-laboratory benefits, level of compliance and safety/toxicity profile of hydroxyurea in a cross section of Nigerian SCD patients.

Methodology

This is a hospital-based, pilot survey among 60 SCD subjects seen at the University of Benin Teaching Hospital, Benin City, Nigeria. Adult SCD subjects in steady (quiescent) state were recruited into the study in a consecutive manner after a detailed explanation of the intended study and consent obtained. The study was conducted according to the standard of the institution's ethics review board. The study was conducted over a period of three months between May and July 2015 at the adult Haematology out-patient department of the hospital. All subjects were diagnosed on the basis of their clinical phenotypes, alkaline haemoglobin electrophoresis and other ancillary tests.

Data was collected from each participant using a structured interviewer-administered questionnaire through an interview process coupled with case file review. Subjects with history of SCD crisis or any other acute illness in the preceding 4-6 weeks were excluded. Data collected included details on bio-data, clinical history of SCD in the preceding one year including previous blood transfusions, awareness about hydroxyurea, haematological parameters, history of hydroxyurea use (dose and duration of use), associated adverse reactions, and possible reasons for non-compliance. Haematological parameters were either carried out on the day of the interview or within the preceding one month of the sampling. Parameters included total leucocyte count (TLC), absolute neutrophil count (ANC), platelet count (PLT), haemoglobin concentration (HB), haematocrit (HCT), Mean corpuscular volume (MCV), red cell distribution width (RDW) and fetal haemoglobin levels (%HbF), where available.

Descriptive and inferential statistics were performed using Statistical Package for Social Sciences (SPSS, version 16), Chicago, USA. Differences in the mean of outcome variables such as annual rates of bone pain crisis (BPC), hospitalizations and haemogram among subjects with history of regular versus irregular/non use of hydroxyurea were compared using Mann Whitney U test. Hypothesis testings were performed at a probability level of 5% (p value = 0.05). Results are presented in frequencies and tables.

Results

The median age of the study participants is 30 years, with a male:female ratio of 1:1.86. Most (86.7%) had haemoglobin SS disease. The annual rates of bone pain crisis, hospitalizations and blood transfusions among the study participants were 3.73, 1.53 and 2.15 respectively. The mean TLC, ANC, PLT, HB, HCT, MCV and RDW among the study participants were 9713/ul, 5366/ul, 286000/ul, 8.26g/dl, 25.42%, 78.93fl, 20.89% respectively. Only two of the subjects had done a fetal haemoglobin assay prior to the study, giving a mean fetal haemoglobin level of 17.6%.

About 57% had heard about hydroxyurea, while 40% (24 subjects) had a used it (Table 1). Only 20 subjects (33.3%) were currently using hydroxyurea according to physician recommendations. Only 4 of these 20 subjects used the drug regularly as prescribed by the doctor. The median duration on therapy was 12 months. Reasons for non compliance with therapy included poor/misinformation, lack of funds to procure drugs, irregular follow-ups, fear of unknown side effects, being tired of drugs and faith healing (Table 1). Four of 24 subjects that used hydroxyurea experienced side effects such as skin rashes, skin hyperpigmentation, blurred vision and dizziness (Table 1).

Table 1: details regarding hydroxyurea therapy

Variables		Frequency(n)	Percentage(%)
History of use			
	Never Used	36	60.0
	Past Use	4	6.7
	Current Use	20	33.3
Duration of use (months)			
	Less than 6 months	8	33.3
	6 months or more	16	66.7
Mean(SEM)=25.71(6.44) , Median=12 , Min=1 , Max=120			
Level of compliance*			
	Regular	4	20.0
	Not Regular	16	80.0
Reasons for non-compliance**			
	Poor/misinformation	3	12.5
	Lack of funds	4	16.7
	Adverse reactions	1	4.2
	Poor clinic attendance	3	12.5
	No reason, feels okay	3	12.5
	Fear of unknown effects like cancer	3	12.5
	Dislike for drugs-Tired of drugs	3	12.5
	Faith healing	2	8.3
Adverse reactions**			
	Skin hyperpigmentation	1	4.2
	Blurred vision	1	4.2
	Dizziness-Lightheadedness	1	4.2
	Skin Rashes	1	4.2
	None	20	83.3

N = 60 (100%), *only 20 subject on current use of hydroxyurea, **multiple responses, 24 subjects with history of Hydroxyurea use

The mean dose at commencement of hydroxyurea therapy was 10.61mg/kg. The mean dose as at the time of the study was 13.49mg/kg (Table 2). The most frequent indication for commencement of hydroxyurea therapy was frequent/severe vaso-occlusive crisis (Table 2). Four of the subjects discontinued hydroxyurea based on doctors' recommendation. Termination of therapy was mostly related to conception/fertility issues (Table 2).

The mean annual rate of BPC among regular hydroxyurea users and irregular/non-users was 2.25 and 3.84 (p value > 0.05), while the mean annual transfusion rates were 1 and 1.57 respectively (p value > 0.05). The mean TLC of regular hydroxyurea users and irregular/non-users was 6050 and 9884/ul respectively. While the mean MCV of regular and irregular/non-users was 103.6 and 77.8 fl respectively. The mean difference of TLC was significantly lower in subjects who used hydroxyurea regularly (p values of 0.024). Mean MCV was significantly higher in regular users, with a p value of 0.018.

Table 2: Physcian's pattern of hydroxyurea prescription

Variables		Frequency(n)	Percentage (%)
Starting dose (mg/kg/day)			
	Less than 10mg/kg	15	62.5
	10 – 20 mg/kg	9	37.5
	>20mg/kg	-	-
Mean(SD)=10.61(3.31), Median=9.01, Min=7.35, Max=17.24			
Current dose (mg/kg/day)*			
	Less than 10mg/kg	5	25.0
	10 – 20 mg/kg	15	75.0
	>20mg/kg	-	-
Mean(SD)= 13.49(3.73), Median=15.05, Min=7.81, Max=17.86			
Indications for commencement of hydroxyurea**			
	Frequent/Severe VOC	19	79.2
	Moderate Disease	3	12.5
	High leucocyte/platelet Counts	1	4.2
	Severe symptomatic anaemia	1	4.2
	Severe/Recurrent ACS	1	4.2
Indications for discontinuation of hydroxyurea			
	Conception/Fertility	3	12.5
	Unbearable Reactions	1	4.2

N=24(40% of all subjects), *20 subjects on current use, **multiple responses

Discussion

The age, sex and haemoglobin phenotype distribution of subjects in this study is comparable to findings from earlier local studies[16,25]. The mean rate of bone pain crisis and hospitalisation in index study were 3.73 and 1.53 per annum respectively. As suggested by prior local studies, Nigerian SCD is still associated with significant pain burden among affected subjects[16]. Approximately 72% experienced at least one episode of BPC in the preceding year. Again, this observation is in tandem with an earlier survey on BPC rate in which 67% of SCD patients experienced one or more episodes in the preceding year[16]. Platt et al reported a slightly lower percentage of about 60% as at 1991 in the US[26]. In a US clinical trial published in 1995, hydroxyurea caused a 44% reduction in median annual rate of painful crisis, with a corresponding decrease in frequency of acute hospitalisations for painful crisis[27]. Hydroxyurea reduced the mean annual rate of BPC by 41% in index study. Hydroxyurea has been shown to shorten duration of hospitalizations resulting from acute pain crisis and the subsequent net requirement for opioid analgesia[35].

There is a moderate level (about 57%) of awareness regarding hydroxyurea among the subjects. Forty percent (24 subjects) had been started on hydroxyurea by physicians, although therapy was discontinued in 4 of the subjects mostly due to fertility related/conception issues. There is a high level of non-compliance among the subjects as only 4 (20%) were regular on therapy. Reasons for non compliance were majorly related to poor health seeking behaviours among the subjects including poor information/misinformation regarding drug use, irregular clinic follow-ups, dislike for drugs. However, economic reason (poor finance) was the more frequent reason for non-compliance with therapy. There is need to evaluate in greater details health seeking practices among Nigerian SCD subjects, with a view to proffering effective solutions for improved care of affected persons.

This survey observed a lower rate of BPC and hospitalization in subjects that used hydroxyurea regularly, though were not statistically significant. However, no particular inferences can be drawn due to the relatively small number of regular users. A well-designed, longitudinal study will be required to evaluate the clinical and laboratory effects of hydroxyurea among indigenous Africans better. As well, the influence of potential confounders such as hemoglobin phenotypes, baseline fetal haemoglobin lev-

els, age, gender, steady state blood cell counts in this survey participants cannot be down played, thus reducing plausible inferential conclusions from this survey.

Similarly, this survey observed significantly lower levels of TLC in subjects who took hydroxyurea regularly. This is a desirable effect since heightened leucocyte and platelet counts has been shown to contribute to chronic morbidities and worse clinical outcomes, even in local settings[28-31]. In this vain, high steady state leucocyte and platelet counts have been suggested as indications for commencement of hydroxyurea[14,19,32]. The mean corpuscular volume of red cells was significantly higher in subjects using hydroxyurea regularly. Again, this is expected as increase in red cell fetal haemoglobin level corresponds to increased MCV. Thus, oval macrocytosis may be an indirect evidence of compliance with therapy. However, only 2 of the subjects had done fetal haemoglobin assay. There is need for relevant authorities to make fetal hemoglobin assay more accessible and affordable in order to facilitate monitoring therapeutic responses.

The recommended initial dose for initiation of Hydroxyurea in SCD ranges about 10 – 20 mg/kg/day[33,34]. Dose escalation at 2.5 to 5 mg/kg is recommended every 4 weeks to 6 months (average 8 weeks), till the maximum tolerable dose is achieved, while the patient is monitored for clinical and haematological responses. As a baseline and during drug titrations, evaluations for organ toxicities (renal and liver function tests) should be conducted every 4 to 8 weeks. The ceiling dose for hydroxyurea in SCD is 35 mg/kg[33,34]. The mean initial dose (at commencement of therapy) of hydroxyurea in the cohort was 10.61 mg/kg/day although more of the subjects started at a dose of less than 10 mg/kg. Despite a median duration of 12 months of therapy, the current dose among the 20 subjects on hydroxyurea was 13.49 mg/kg. This suggests that dose escalation or achievement of maximum tolerable dose was not a major therapeutic target among prescribing physicians. This trend may be related to exercise of caution as regards marrow suppression and organ related toxicities, which could worsen patient morbidities. Possibly, irregular use of the drug, as well as the insignificant dose escalation may be related to low purchase power (insufficient funds) among affected patients, who are majorly persons of low or middle socio-economic class.

Three of the subjects with history of hydroxyurea use exercised fear regarding unknown adverse effects of hydroxyurea such as its potential carcinogenic and teratogenic effect, being a cytotoxic. However, 83.3% of the subjects who used hydroxyurea reported good oral tolerance without toxicities. Others reported known side effects such as skin hyperpigmentation and rashes. One of the subjects reported blurring of vision and therapy had to be discontinued. Another patient reported dizziness but symptom resolved with dose reduction. Over the past two decades, studies have consistently shown a good safety profile with mild reversible short term toxicities[36,37]. Though there is a theoretical risk, there is no substantial evidence that hydroxyurea increases the risk of blood cancers or solid tumors relative to the general population[20,37]. Prior to initiation of therapy, treatment goals must be defined and detailed education on the drug must be provided to the patient. Patients should be reassured of the safety profile of hydroxyurea based on relevant data/existing literature. Patients should be counseled on regular follow-up to monitor for the expected clinical and haematological responses. Effectiveness of treatment with hydroxyurea is related to compliance with daily use and patients should be counselled as such[34]. Absence of response after 12 months of monitored therapy is an indication to discontinue hydroxyurea, about 10 - 20% may be non-responders[38].

Conclusion

Hydroxyurea shows significant prospects in ameliorating Nigerian SCD. However, there is still a relatively low level of awareness, irregular use and absence of/poor compliance with standard protocols in Nigeria. Large-scale longitudinal studies and clinical trials are needed to optimize the indications, dosing and safety profile of hydroxyurea in the indigenous Nigerian population. Physicians and Nigerian SCD patients need to be educated continually on the clinical utility of hydroxyurea. Barriers to its use should be elucidated through further research and proper interventions should be engaged. Governments, NGOs, Support agencies, pharmaceutical companies and other relevant stakeholders should engage in more active participation regarding maximising hydroxyurea therapy in Nigerian SCD through advocacy, better funding, continuous education/public enlightenments and other requisite strategies.

Conflict of interest

None to declare.

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