Hydroxyurea in children with sickle cell disease in a resource-poor setting: Monitoring and effects of therapy. A practical perspective

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Abstract

Abstract Background: Effectiveness of hydroxyurea (HU) in SCD is well established. Unanswered questions persist about use in African children in terms of acceptability and monitoring. We determined real-life user-barriers, safety and effects of therapy among children using HU in Nigeria. Methods: We retrieved and reviewed case notes of children on hydroxyurea (10-15mg/kg/day followed by dose escalation) from January 2017 to June 2019, checked for adherence to drugs, clinics and laboratory tests; starting dose, toxicity and benefits (hematologic, clinical, parental satisfaction). A questionnaire complemented case note findings. Results 116 patients received hydroxyurea (mean dose of 18 mg/kg/ day). Improvement in general well-being was 91.25%, reduction in bone pain 83.3%, hospital admissions 71.9%, abdominal pain 62.3%, blood transfusion 56.1%. Sixteen percent voluntarily stopped HU because of cost and side effects. Sixty-seven percent of parents complained about daily drug use, frequency and cost of monitoring. Adherence to daily HU was 88.8%, doctor's appointments 22.8%, hematology tests 17.5%, organ function 32.5%. Five patients had mild neutropenia. No significant hepatic or renal toxicity occurred. Common side effects were abdominal pain (18.4%) and headache (13.2%). Significant increase in hemoglobin, fetal hemoglobin, MCV and reduction in absolute neutrophil counts occurred. Conclusion: Hydroxyurea at 10-15mg/kg/day is safe, effective and acceptable to parents. Monitoring is challenging. Care-giver education, support services, staff training, HU clinics may improve utilization. HU protocols that reduce monitoring and yet provide good clinical and laboratory benefits are necessary. This study adds to the implementation science strategies that is needed to increase HU use in Nigeria.

INTRODUCTION

Sickle cell disease (SCD) is a chronic debilitating genetic disorder with significant global public health implications[1]. Progress made so far in understanding of the molecular and clinico-pathological basis of the disorder has not been matched with corresponding treatment modalities[2,3]. Effective and accessible treatment globally is based on use of blood transfusions, antibiotics, analgesics and hydroxyurea in the context of a comprehensive approach to care[4,5]. Bone marrow transplant and gene therapy offer tangible hope of cure but are very expensive and inaccessible to many patients. Comprehensive care is reported as largely responsible for the improved quality of life and survival in people with SCD in resource rich countries[1,6]. With improved diagnosis and management, over 98% of children with SCD in resource -rich countries survive to adulthood with a life-expectancy of 53 years for men and 58.5 years for women[7,8]. On the contrary, SCD remains a huge economic and psychosocial burden in sub-Saharan Africa (SSA) and for most families in Nigeria, partly because of absence of accessible quality health care and public health interventions[2,4,9].

In Nigeria, with an estimated disease prevalence of 2% , a carrier rate of 21%(NDHS 2019) and a projected global increase in annual delivery of infants with SCD to 400,000[10], the scourge of the disease will increase if interventions are not put in place. The benefits and safety of hydroxyurea as a disease-modifying agent in the treatment of SCD in children and adults, is well documented and is in common use in resource-rich countries[11,12,13,14]As part of a comprehensive care for SCD that incorporates early detection through neonatal screening, penicillin prophylaxis, immuno-prophylaxis and caregiver education on health maintenance and splenic palpation, hydroxyurea has been shown to significantly reduce acute painful episodes, hospitalization, transfusions, and protect organs with consequent improvement in quality of life and ultimately, survival[12,15,16] . In 2014, the National Heart, Lung and Blood Institute recommended offering children hydroxyurea from 9 months of age irrespective of their clinical symptoms[17].

Although Nigeria has the highest global burden of the disease with over 150, 000 SCD deliveries annually and 50-90% dying before their fifth birthday, as reported for most parts of SSA[4,18] many centers still lack the full complement of a comprehensive care that includes hydroxyurea therapy[19,20,21,22]. Reasons adduced for paucity of use include inadequate knowledge and experience on the part of healthcare providers, lack of appropriate treatment guidelines(including paediatric guidelines), lack of data on the impact and magnitude of SCD in resource-poor settings, concerns about response to hydroxyurea in children as influenced by issues of geography, poverty, health literacy, nutrition, infestations, underlying host disease and immunological response[5,19,23,24]. There are also concerns about affordability (including multiple laboratory tests and hospital visits) and sustainability of hydroxyurea within the weak health system that characterizes most health institutions in Nigeria[19,21,22]. These issues raise questions about adopting results of hydroxyurea use in resource-rich countries to Nigeria or SSA as a whole.

In 2016, the NOHARM clinical trial in Ugandan children with SCD reported extensively on the safety and effectiveness of hydroxyurea in malaria-endemic Uganda even though optimum dosing and monitoring regimens were not explored[25]. In 2018, a larger African-based study on hydroxyurea, involving children with SCD in four countries in SSA (Angola, Democratic Republic of Congo, Kenya and Uganda) showed that hydroxyurea treatment was feasible, reasonably safe, and had both laboratory and clinical benefits[23].

Some recent studies about hydroxyurea uptake in Nigeria[19,26,27]have demonstrated the clinical effects of hydroxyurea that may be comparable to that observed in resource-rich countries and other African countries. Lagunju et al, while working on Nigerian children with SCD reported the benefits of hydroxyurea in primary and secondary prevention of stroke[28,29]. Focus of research is consequently on increasing HU uptake. Adeyemo[24] and other Nigerian researchers[5,30,31] have reported extensively on provider-related barriers to HU use but little is, known about user- related barriers like feasibility (adherence to drug use, regular hospital visits, laboratory tests and sustainability of affordable hydroxyurea). As Nigeria and other SSA countries begin to devote more resources to the care of patients with SCD, survivors would be on the increase with a corresponding increase in morbidity making it compelling that hydroxyurea, an affordable and cost-effective treatment option, be used to boost their quality of life and survival[32]

This retrospective review deals with issues of acceptability, availability, monitoring, safety and efficacy of hydroxyurea that constitute barriers to HU uptake from the user perspective. The study seeks to answer the following research questions: Can patients comply with daily use of hydroxyurea? Is monitoring of therapy and dose escalation possible? Is 15 mg/kg/day a safe starting dose of hydroxyurea for children? Does HU produce adverse effects? Will daily use of hydroxyurea produce clinical and laboratory benefits? Are parents satisfied with the use of hydroxyurea? The study may identify modifiable factors that hamper use of hydroxyurea among paediatric sickle cell population in Nigeria.

Patients, Materials and Methods

This study is retrospective in design and involves the first set of patients to use hydroxyurea in the pediatric hematology unit of the University of Abuja Teaching Hospital from January 2017 to June 2019. The unit offers comprehensive care to patients with SCD that includes structured health education, prophylaxis for malaria and pneumococcal infection with proguanil and penicillin V respectively. Everyone received daily

folic acid and/or non-iron containing multivitamins. All patients had childhood immunizations according to the National Program on Immunization but less than 25% of the patients could afford the extra immunization recommended for SCD (pneumococcal, meningococcal and typhoid vaccines). The unit does not have a newborn screening program and patients do not have access to routine transcranial doppler screening. Diagnosis of SCD was by hemoglobin electrophoresis and High Performance Liquid Chromatography.

Indications for hydroxyurea therapy: All the patients aged 1 year to 18 years who had Hb F values of less than 10% or had a severe manifestation of SCD such as stroke, acute chest syndrome, repeated admissions/transfusions as well as patients who expressed interest in HU were eligible for this pilot trial[17]. Patients with severe debilitation were excluded from HU use.

Pre-HU Evaluation : An initial sampling of parental opinion about HU revealed unfamiliarity with the drug while a few were concerned about side effects, affordability, and sustainability. Consequently, patients and families had 2 awareness programs that focused on effects of HU and dispelling myths. Patient information leaflets were provided. Families who indicated interest in using HU returned for another session that allowed them to learn more about monitoring and ask questions emanating from the leaflet. Those who expressed commitment to follow-ups were offered therapy. They did baseline evaluations: Hb F levels, complete blood count, liver function tests (serum bilirubin, alanine transaminase, aspartate transaminase and alkaline phosphatase), renal function tests (serum urea nitrogen and creatinine).

Dosing of HU/escalation: Hydroxyurea (Oxyurea) was locally sourced and patients started on 15mg/kg/day or 10mg/kg/day for steady state Hb of $<$ 6gm per dl. The protocol[17,33]aims to achieve symptomatic relief and hematologic response (Hb of 10gm/dl) with the lowest dose of HU that is sustainable over 12weeks (therapeutic dose). Dose escalation was 3 to 6 monthly to a maximum of 25mg/kg/day as appropriate. HU was available in capsules of 100mg, 250mg and 500mg and the hospital pharmacy compounded suspensions fortnightly for infants and toddlers. HU was affordable at an initial cost of Naira 600=$1.70 for 100mg pack of 30 capsules; Naira 800= $2.25 for 250mg pack of 30 capsules; Naira 1100= $3.07 for 500mg pack of 30 capsules. Cost of drug increased by 45% to 62.5% during study period because of hospital logistics but some patients could access a health insurance with annual premium of Naira 15000 ($41.00) that covered most laboratory tests and HU.

Monitoring and Toxicity : Patients were seen in the clinic biweekly for one month (for complete blood counts) and then monthly. Liver and renal function tests were done 3 monthly for 6 months, then 6 monthly for evidence of toxicity (13 doctor's appointments and 15 laboratory tests in a year). Hb F quantification was repeated at 1 and 2 years of therapy due to cost. During each monitoring visit, patients were asked about HU acceptability, adherence, side effects and occurrence of acute events. A physical exam was done every 3 months. Toxicity was defined as hemoglobin of [?]5g or 20% decline from baseline (in the absence of any other cause for the decline), platelets of less than 80 x 10^9 /L, absolute neutrophil count of less than 1.5 x10^9 /L, alanine transaminase of twice the upper limit of normal for age or double the baseline value, creatinine of 2 times baseline value or more than 1 mg/dl. For toxicity, HU was either reduced by 5mg/kg/day or stopped for 1 to 2 weeks for values to normalize

Data Collection: Outcome variables for the study are user barriers (adherence to monthly clinic visits, completion of laboratory tests, adherence to daily HU), safety (safe starting dose/escalation, reported and observed side effects), benefits: hematologic (Hb F, Hb, white cells, platelets, mean corpuscular volume), clinical (reduction in acute painful episodes, hospitalization, transfusion, improved general wellbeing) and parental/patient satisfaction.

Data were initially recorded in patients' case files and later transferred to a proforma before extraction for analysis.

Tracking patients/Missed visits: The unit relied on case note documentations and nurses' appointment registers which were often incomplete or missing. We developed a questionnaire to capture information on compliance to clinic visits, laboratory tests, HU use and parental satisfaction with HU therapy. The questionnaire, which was administered by a trained research assistant, consisted of 12 items and took about

5 to 8 minutes to complete (appendix1). Patients' responses were matched with available information in the case notes.

Ethical approval was given by the UATH ethical review board (UATH/HREC/PR/2019/057) and parents gave consent to provide extra information to collaborate the case note documentations.

Statistical Analysis: Analysis was with statistical package for social sciences IBM [SPSS] version 21 (Armonk, NY 2012). Initial descriptive analysis of all variables was done using means and standard deviations for continuous variables (laboratory data) and frequencies and percentages for categorical variables (user barriers, safety, clinical benefits and parental satisfaction). The annual mean values of the laboratory variables were compared with patients' baseline values pre-HU using the paired Student's t-test. Statistical significance was set at 0.05.

Results

Patient characteristics: There were 66 males and 50 females. Most of the patients were HbSS (96.5%), 3 were HbSβ^0thal (2.6%) and 1HbSC (0.9%). The median age at initiation of HU was 9.5 years. Average duration of HU therapy was 18 months (range 12 months- 33months) with an average HU dose of 18.5 mg/kg/day (range of 10 mg-32mg/kg/day). Only 1 patient with persistent pain received HU dose at 32 mg/kg/day and 3 patients with stroke received 25 mg/kg/day.

Patient retention: 116 patients were offered HU from January 2017 to September 2019. Eighteen patients (15.6%) dropped out within 12 months for: lack of funds (50%), family issues (22%), drug not working (16.7%), bleeding gums (5.6%), splenic sequestration (5.6%). Seventeen other patients (14.7%) stopped because of family logistics and lack of funds but resumed therapy after counselling. Three patients (2.6%) relocated to other states and another three had missing baseline data. Only patients who had baseline laboratory data and who had used hydroxyurea for at least 6 months were used for statistical analysis (N= 89). Patients who had missing data at various stages of the analysis were analyzed for their available data. Questionnaire was administered to 114 families (66 Males, 48 Females) including those who stopped hydroxyurea. Two patients who relocated could not be reached. Response rate was 100%.

User barriers: Table 1

Adherence to therapy: Ninety-five (88.8%) patients reported taking hydroxyurea daily. Among defaulters, six (50%) reported failing to take for 3 months (poor compliance). Table 1 summarizes c**ompliance with doctor's appointments and laboratory tests.**Only 26 patients (22.8%) complied with 13 doctor's appointments in 1 year. Twenty patients (17.5%) and 37 patients (32.5%) completed expected hematologic and organ function tests respectively.

Safety : **Starting dose** : Most patients (96.5%) received 15 mg/kg /day of HU. Four patients (3.5%) with Hb <6gm/dl received 10 mg/kg/day. **Dose escalation:** Escalation of dose was not consistent for logistic reasons and many patients were on the starting dose for over 6 months. Routine escalation did not go above 20 mg/kg/day for about 90% of the patients. **Side effects:**Reported side effects are shown in Table 2. Therapy was stopped for 3 months in a patient with persistent abdominal pain and was later resumed at a lower dose and gradually escalated. One child had accidental overdosage of HU suspension (about 105mg/kg/dose) and therapy was suspended because of transient marrow suppression. Changes in mean serum alanine transaminase and serum creatinine at baseline and 18 months are not statistically significant (p=0.312; p=0.122) respectively. Table 3. No patient had dose-limiting toxic effects regarding thrombocytopenia, alanine transaminase or serum creatinine. Mild, transient neutropenia (ANC of 1.34 to 1.5x 10^9/l) occurred in 5 patients (5.6%) that resolved with dose adjustment.

Hematologic : Baseline values showed anemia (mean of 7.1±1.3g/dl), low Hb F (mean of 8.2±0.6%) and leukocytosis (mean of 13.7±0.5 x10^9/l). After 24 months of therapy (n=40), there was significant increase from baseline in Hb (1.6g/dl, 95% CI 1.1 to 1.7), the mean corpuscular volume (9 fl, 95% CI 5.2 to 11.4), foetal hemoglobin (5.3%, 95% CI 2.4 to 8.2). Significant increases were also documented at 6 months, 12 months and 18 months of therapy (Table 3). There was a progressive and significant reduction in white cell

count (-4.1x10^9/l, 95% CI -4.8 to-2.4), absolute neutrophil count (-2.3 x 10^9/l, 95% CI -2.1 to -2.9) from baseline through 24 months. Table 4. There was a progressive decline in total bilirubin (TB) over the 2-year period.

Clinical effects: Majority 104 (91.2%) of the patients reported an improved general well-being and symptomatic relief Table 2.**Parental satisfaction:** Most 102 (89.5%) of the parents expressed satisfaction with use of hydroxyurea and would like to continue its use. Table 5 summarizes parental concerns about hydroxyurea which includes cost of laboratory tests, availability and cost of drugs.

Discussion

In this retrospective review of a short-term use of HU in children with SCD, we found that a starting dose of HU of 10-15 mg per kilogram body weight per day is safe, effective and feasible except for challenges posed by monitoring and dose escalation. Majority of the patients reported compliance to daily use of HU but were unable to keep all doctor's appointments and laboratory tests. Most patients reported improvement in well-being and sickle-related symptoms but expressed concerns about cost of drugs, frequent laboratory tests and hospital appointments. Common side effects reported were headaches and abdominal pains. Few parents either wanted to discontinue use of HU or were undecided about future use. There was good hematologic response to HU even among children with very low stable state hemoglobin.

The REACH[23] and the NOHARM[25]studies, as well as some Nigerian studies[26–28], have reported on the safety, laboratory and clinical response of African children to HU that compares to the results of this retrospective study. Our study, in addition, reports on user-related barriers to a sustainable HU use from the paediatric point of view.

Our data show that contrary to concerns about feasibility of a sustainable HU use in Nigeria and Africa in general, many care givers welcome the use of HU in their patients and made concerted efforts to comply with drug use. The increasing mean MCV reported in this study corroborates the good drug compliance reported by parents even though many complained about the stress of daily consumption of HU. Some local studies that provided free HU for patients observed that many patients stopped HU after the study because of cost and unavailability and opined that offering free HU to patients would improve uptake in resource-poor settings (oral communication). Our study showed that an affordable and sustainable drug supply, anchored on proper health education enhanced uptake of HU. A hike in drug price during the study resulted in patient protest and only patients with an insurance policy afforded it with ease. This underscores the importance of sourcing affordable HU for sustainability of therapy.

Worse challenges to a sustainable HU uptake were frequent laboratory tests and doctor's appointments. In this study, patients were subjected to monthly doctor's appointments and laboratory tests because of the poor health-seeking behavior of most families. Parents who accept HU but do not come for follow-up expose their children to risk of drug toxicities. With steady and intensive health education given at each visit, obvious clinical response to HU and the unit 24-hour phone access to patients for appointment reminders, many families appreciated the reason for the frequent monitoring and showed willingness to improve compliance. Most standard HU protocols require frequent monitoring especially at the onset until patient is on a stable dose. Adewoyin[19] and Aliyu[31] in separate reports attributed low HU uptake in Nigeria partly to cost of drug and follow-up visits in their adult and non HU using patients. Akinshete et al[26] reported 6 monthly monitoring of his paediatric patients on HU because of cost. Ofakunri et al[27] in Jos monitored laboratory tests monthly under a protected research environment with good compliance. There is no consensus on frequency of monitoring for the African user that will reduce cost without exposing users to toxicity. Cost of HU and follow-up visits remain common barriers for both adult and paediatric patients who use HU in real-life situations

In keeping with reports from resourceful centers with many years of experience HU, no major side effects were reported from patients within the 2-year period. In our study, headache was commonly reported at onset of therapy but improved with use. Patients with recurrent abdominal pain were advised to take medication at bedtime and many subsequently did well. This observation adds to other reports from Nigeria[26],[27] that

showed no worsening safety margins of HU in Africa because of host and environmental factors and calls for a wider use of HU in African children with SCD[21,27,34] Doses at 10-15mg/kg of HU was a safe starting dose that resulted in significant clinical and laboratory effects even with minimal dose escalation. Jain and co-workers in India[35] reported good response of patients to 10mg/kg/day of HU even though many had higher baseline Hb F values compared to patients in our study. These observations may be an indication of good hematologic response to moderate doses of HU and underscores the use of therapeutic dose rather than a maximum tolerable dose that may expose patients in resource poor countries to toxicity where monitoring may be suboptimal. HU dosing in our study failed to produce a mean Hb of 9-10g/dl and HbF level of at least 20% or marrow depression with ANC of 2 to 4000 which is associated with sustainable clinical effect[36,37,38] even though most of our patients had good clinical response within the short duration of therapy. Our focus is on achieving good clinical response without overly intensive dose escalation[39]. Researchers in Africa and Asia are reporting effectiveness of intermittent[40] or low-fixed dosing[35,41] of HU in SCD subjects. In Nigeria, Titilola[42] reported clinical and laboratory response to a low fixed dose of HU in adult patients with SCD. This approach may ameliorate the challenges of HU monitoring. Reduced frequency of HU use will reduce cost, ensure better compliance and may represent a viable option for improving HU uptake in Nigeria and sub-Sahara Africa.

The limitation of this study lies in its retrospective nature and the use of manual documentation of patient medical records which made retrieval of source documents laborious. The hospital, however, is in the process of migrating to electronic medical information system which will make future studies easier. The strength, nonetheless, lies in the real-life circumstances of the review which provides practical and real-time insights and possible solutions compared to the protected circumstances of a structured research.

In conclusion, there is a compelling need for the adoption of HU as an integral part of the standard of care for children with SCD in Nigeria. Challenges of sustaining HU use are many but can be improved by on-going patient and parental health education, provision of affordable and sustainable supply of HU and subsidized laboratory tests through affordable health insurance schemes. This study joins others to attest to the good clinical efficacy and safety of HU while highlighting some user- barriers to a sustainable HU use. It will add to the implementation science strategies and training that is needed to increase HU uptake among children with SCD in Nigeria.

Future research may focus on determining effective intermittent and fixed- dosing protocols that would reduce monitoring and cost of HU and still provide good clinical and laboratory benefits to users.

Conflict of Interest Statement: None

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

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