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Clinical Outcomes, Barriers and Facilitators to Hydroxyurea Use for Sickle Cell Anemia: A Mixed Method Study at Muhimbili National Hospital, Tanzania

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Abstract

Background

Tanzania is among the five countries with the highest estimated number of newborns with Sickle cell disease (SCD) in sub-Saharan Africa. Hydroxyurea (HU) is recommended for infants from 9 months of age, all children and adolescents with Sickle Cell Anaemia (SCA) however it's utilization in clinical practice is not optimal.

Materials and Methods

A mixed method study was conducted from October 2019 to January 2020 among children with SCA attending a tertiary paediatric haematology clinic at Muhimbili National Hospital. Children between the age of 6 months and 18 years were consecutively included based on inclusion/exclusion criteria set for the quantitative study. Structured questionnaires were used to collect data based on the purpose of the study. Caregivers of children with SCA, clinicians, and pharmacists participated in four focus group discussions to explore barriers and facilitators to hydroxyurea (HU) use. A sequential explanatory design was used, quantitative data analysis was conducted using SPSS (version 21) and content thematic approach for the qualitative data.

Results

Out of 400 children enrolled, 59% were males with a median age of diagnosis at 2 years and 8 months (IQR 1- 4). The coverage gap to initiation of HU was 65% (260/400) and children who were on HU being less likely to be transfused (6.4% Vs 14.6%, p value < 0.05), and had a trend of lesser hospitalization, (9.3% Vs 12.3%, p value 0.33) compared to non-users respectively. Common reasons holding the coverage were caregiver's unawareness (61%) and lack of medical insurance/affordability (29%). Qualitative learnings showed facilitators for HU use included improved symptoms, good compliance, and financial stability/active medical insurance. Even with medical insurance, longer time to get special permit to access it and fare/monthly clinic attendance because of limited supply were among the barrier to use HU. Poor knowledge/awareness for both parents and clinicians, and fear of side effects were also reported.

Conclusion and recommendations

Children with SCA were diagnosed late, and coverage for HU use was low. Increasing awareness, effective use of medical insurance and improving access of hydroxyurea within the health system would be vital for quality care among children with SCA.

Keywords: *Hydroxyurea, Clinical outcome, Utilization, Barriers, Facilitators, Sickle Cell Anaemia.*

Introduction

Sickle cell Anaemia (SCA) is among the most common inherited haematological diseases, accounting for more than 300,000 newborns annually, with the highest burden in Sub Saharan Africa (1). The global and local estimates of SCA speculate an increasing burden and excess mortality (2, 3), necessitating focus on comprehensive care and developing strategies for curative services (4). Even though national policy and management guidelines for SCA exist (5, 6), Tanzania like many other sub-Saharan countries has been slow in administering hydroxyurea (HU) despite evidence on reducing morbidity and improving survival (7-10). There have been an increased efforts to expand the national health insurance program (NHIF) coverage for HU use at all levels of care (11) which will substantially increase utilization.

HU is a disease modifying drug approved by United States Food and Drug Administration in 1998 which induce production of foetal haemoglobin, preventing complications, improving quality of life and survival among children with sickle cell disease (7, 12). It has been shown to have laboratory and clinical benefits including increasing both adult and fetal haemoglobin, reducing vaso-occlusive crises, rate of blood transfusion and hospitalization (8, 13).While strong evidence exists and HU is recommended to be initiated for infants from 9 months of age, all children and adolescents with SCA regardless of clinical severity, studies still suggest HU is underutilized in actual clinical practice (14-16). It has been documented in project settings among paediatric patients, access to HU use via insurance but not cash was associated with improvement in clinical and haematological outcomes (16). Patients with SCA in Tanzania are usually diagnosed late, often with life threatening complications, increased hospitalization and blood transfusions and decreased quality of life (17) and may not be achieving maximum tolerated dose on HU due to the fear of side effects and lack of monitoring (18, 19). This study aimed to determine clinical outcome, barriers and facilitators to HU utilization among children with SCA attending a tertiary clinic in Tanzania.

Materials and Methods

Study setting and design

A hospital based descriptive cross-sectional study with a mixed method approach utilising a sequential explanatory design was conducted at paediatric haematology clinic at Muhimbili National Hospital, a tertiary hospital, situated in Dar-es-Salaam, Tanzania. It has a 1500 bed capacity and serves approximately 1200 outpatients per day in different specialties.

Study Population and data collection

The quantitative study included 400 children aged between 6 months and 18 years estimated from the Cochran's formula using proportion of SCA related vaso-occlusive crisis of 37.6%

(20) from October 2019 to January 2020. After written informed consent, and with an aid of a structured questionnaire with three parts, care givers of children with SCA were interviewed in Swahili language on (i) Socio demographic information (ii) Any complications experienced in a year (iii) The third part focused on those children on HU to see the date/age of initiation, criteria of being initiated and the facilitators to HU use. Additional information such as details on methods of diagnosis, hospitalization, and associated complications was collected from the patient case notes.

Eligible criteria for HU used in this study were (i) Infants under nine months with symptomatic disease such as vaso-occlusive crisis and dactylitis (ii) Three or more moderate to severe vaso-occlusive episodes in one year, (iii) Chronic pain that interfere with daily activities of life or quality of life such as playing with peers, and frequent school absenteeism, (iv) History of acute chest syndrome, (v) Three or more blood transfusions per year and (vi) History of stroke/cerebral vascular accident (20, 21). Adherence to HU use was ascertained by modified Morisky scale (22).

A sequential explanatory design was used (23), four focus group discussions involving care givers with children not on HU, care givers with children on HU, clinicians and pharmacists, were conducted for qualitative data collection. Six participants in each group were purposively selected making a total of 24 participants. The main aim of the FGD was to perceive the barriers and facilitators to HU use. The clinicians' group included one paediatrician, four intern doctors and two registrars; one pharmacy supervisor, four intern pharmacists and two dispensing officers were in the pharmacist's group.

All FGD's were conducted in a quiet room near the haematology clinic, facilitated by the principal investigator as the main moderator and a note taker. Guiding questions and preliminary quantitative results were used to facilitate the discussion and gaining a better understanding of the barriers and facilitators to HU use. The discussion lasted for about 30 to 60 minutes inclusively subject to data saturation. FGD with caregivers of children with SCA was conducted after their clinic visit using Swahili language, while for the clinicians and pharmacists' English language was used. Notes were jotted down during the discussions and were typed/translated to English in a word document.

Data Analysis

Quantitative data was entered in the statistical package for social science (SPSS) version 21. Frequency tables were used to summarize the data. Continuous variables were described as median with interquartile range. Differences in proportions were tested using the chi square

test and fisher's exact test where applicable. A p-value of equal or less than 0.05 was considered statistically significant.

Content thematic approach was used for qualitative data. The process involved familiarization of the data through re-reading translated expanded notes; initial coding of the notes, identifying as well as reviewing and naming the initial themes; data interpretation and finally writing up the report by the principal investigator himself guided by the qualitative supervisor

Results

A hospital based descriptive cross-sectional study with a mixed method approach utilising a sequential explanatory design was conducted at paediatric haematology clinic at Muhimbili National Hospital, from October 2019 to January 2020 to determine clinical outcome, barriers and facilitators to HU utilization.

Quantitative Results

Among 406 children who attended paediatric haematology clinic, 6 care givers declined to participate in the study, hence 400 children were enrolled.

The median age of the participants was 6 years (IQR 3-10) and male were predominant (58.8%). The median age of diagnosis was 2 years and 8 months (IQR 1-4) and 87% of the children were diagnosed by Hb electrophoresis (See Table 1 and 2).

Table 1: Social Demographic characteristics of enrolled children with SCA (N=400)

Variable	Frequency (%)
Age	
<1 year	15 (3.8)
1-5 years	155 (38.8)
6-11 years	159 (39.8)
12- 18years	71 (17.8)
Median age	
6 years (IQR 3-10)	
Sex	
Male	235 (58.8)
Female	165 (41.3)
Residence by Region	
Dar-es-Salaam	367 (91.8)
Others	33 (8.2)

Out of 400, 240 children (60%) had at least one hospitalization in the previous year. The three common reasons for hospitalizations were, bone pain (31.7%), severe anemia (27.5%) and sepsis (16.7%) as summarized in Table 2.

Table 2: Diagnosis and related events of enrolled children with SCA (N=400)

Variable	Frequency (%)
Method of diagnosis	
Sickling test	30 (7.5)
Hb electrophoresis	349 (87.3)
HPLC	21 (5.3)
Place of diagnosis	
MNH	361 (90.3)
Others	39 (9.7)
Age of diagnosis	
< 1 year	79 (19.8)
1-2 years	68 (17.0)
2-5 years	193 (48.3)
> 5 years	60 (15)
Median age at diagnosis	
2 years, 8 months (IQR 1-4)	
Number of hospitalizations past one year (N= 240)	
< 3 hospitalizations	195 (81.3)
≥ 3 hospitalizations	45 (18.8)
Number of blood transfusions in 1 year (N= 160)	
< 3 BT	113 (70.6)
≥ 3 BT	47 (29.4)
Common reasons of hospitalizations	
Bone pain	76 (31.7)
Severe Anemia	66 (27.5)
Sepsis	40 (16.7)
Acute chest syndrome	16 (6.7)
Stroke	13 (5.4)
Others*	29 (12.1)

**Others: Chronic pain, Priapism, Avascular necrosis of the femur*

Proportion of children with SCA not initiated on HU

Among the 400 children with SCA enrolled in the study, 260 (65%) of children were not initiated on HU despite having indication. The common reasons not being initiated were mainly caregiver unawareness (60.8%), and lack of insurance/affordability (29.2%), See Figure 1.

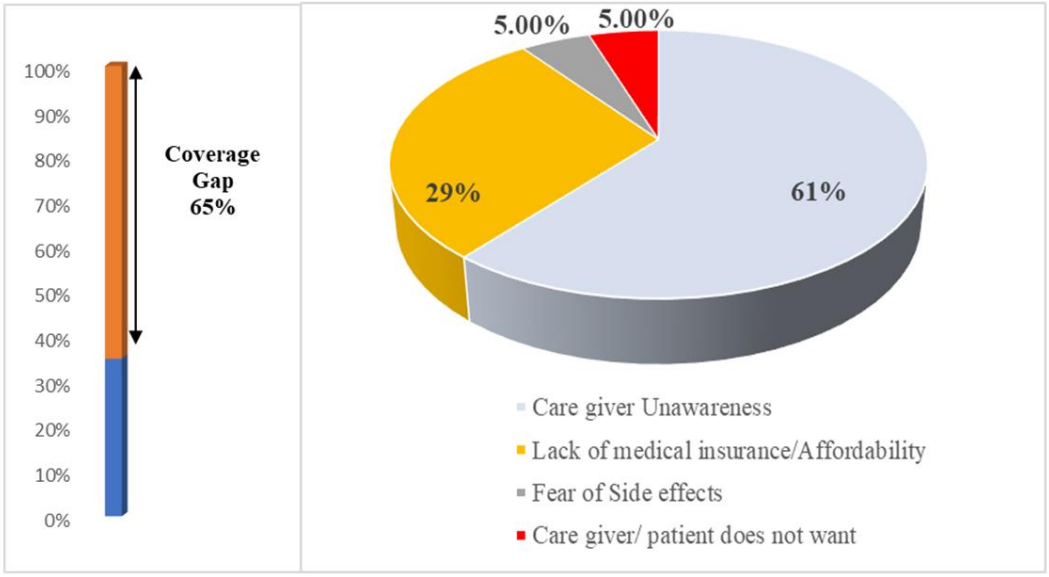


Figure 1. Reasons for not being initiated on HU

Clinical outcomes of HU use among children with SCA

Out of 400 children enrolled, 140 (35%) children were on HU. The median age of initiation and duration on HU were 7 years (IQR 4-10), and 1 year (1 month-14 years) respectively. The duration of majority on HU (up to 62.2%) were between 1 to 3 years, 37.7% were less than a year and 7% at 4 years and above. The adherence as per modified Morisky scale was above 96%. The most common reasons of initiation were > 3 vaso occlusive crisis (VOC) in a year (49%), stroke (23%), > 3 blood transfusion (BT) in one year (15%) and acute chest syndrome (ACS) (8%).

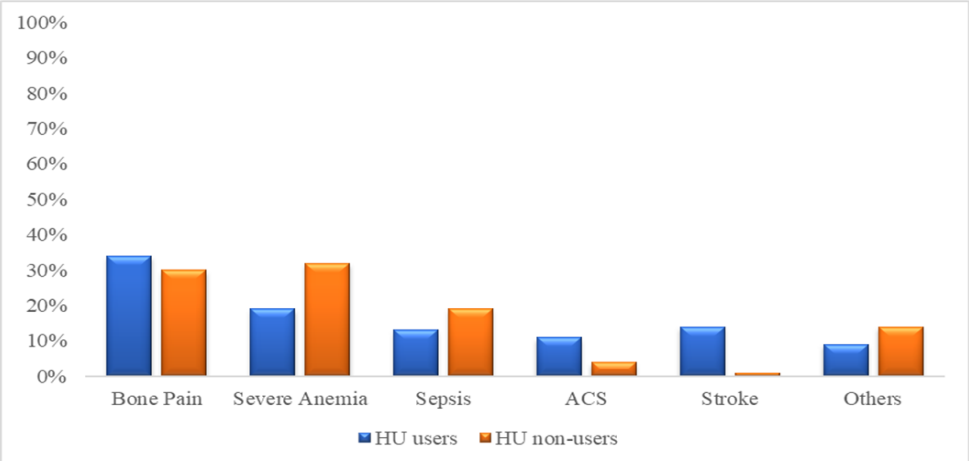
Of the 160 children who received blood transfusion, children who were using hydroxyurea were less likely to be transfused than those not on hydroxyurea, 90 (64.3%) Vs 150 (57.7%) with p-value = 0.05. Likewise, of the 240 children who were hospitalized at least once, the number of hospitalizations were far more common on children not on hydroxyurea 108 (41.5) Vs 52 (37.1), as summarized in Table 3, although not statistically significant. The proportions of sickle related complications such as anaemia and sepsis were more marked on the children not on hydroxyurea (See Figure 2).

Table 3: Clinical outcome of children with SCA according to the HU status

Variable	Hydroxyurea Status			
	Non-HU users (N = 260)	HU Users (N = 140)	Total (N = 400)	P-Value
***Attend school regularly for past one year**				
Yes	123 (47.3)	68 (48.6)	191 (47.8)	
No	137 (52.7)	72 (51.4)	209 (52.2)	0.809
****Ability to play with peers**				
Yes	202 (77.7)	87 (62.1)	289 (72.3)	
No	58 (22.3)	53 (37.9)	111 (27.7)	0.001
Number of hospitalizations in past one year				
None	108 (41.5)	52 (37.1)	160 (40.0)	
1-2 Hospitalizations	120 (46.2)	75 (53.6)	195 (48.8)	
≥ 3 Hospitalizations	32 (12.3)	13 (9.3)	45 (11.2)	0.33
Number of BT in one year				
None	150 (57.7)	90 (64.3)	240 (60.0)	
1-2 Blood transfusions	72 (27.7)	41 (29.3)	113 (28.2)	
≥ 3 Blood transfusions	38 (14.6)	9 (6.4)	47 (11.8)	0.05

**Attend school regularly means takes up a seat in class they're enrolled in, unless prevented by illness.*

***Ability to play in a child is a mere spontaneous act of engaging with other children of similar age showing interest in both the activity and other children involved in playing.*



*Others: Chronic pain, priapism, Avascular necrosis of the femur

Figure 2. Proportion of SCA related events among HU user's Vs non-users

Qualitative Results

Across all the discussion groups, three main emerging themes were discussed: 1) knowledge on hydroxyurea, 2) perceived barriers and 3) perceived facilitators as summarized in Table 4.

Table 4: Perceived barriers and facilitators for HU use

Overarching themes	Sub-themes
Knowledge of hydroxyurea	• Awareness • Usefulness
Perceived barriers	• Unawareness of caregivers on hydroxyurea • Cost/lack of medical insurance • Fear of side effects • Availability of hydroxyurea
Perceived facilitators	• Good compliance • Improving symptoms • Active medical insurance/financial stability

Knowledge of HU

Almost all FGD participants (caregivers of children on HU, clinicians, and pharmacists) had good knowledge in terms of its usefulness.

> *"Yes, hydroxyurea is effective in SCA, 3 severe Vaso-occlusive crises in a year, recurrent Blood transfusion, acute chest syndrome, priapism, stroke are some of the criteria for hydroxyurea initiation." (P2, FGD-Clinician, Intern doctor)*

Most of the care givers reported their children had been started on hydroxyurea due to frequent pain episodes and they reported similar clinical outcomes, improving the quality of life of their children.

> *"Yes, currently he can attend school regularly; pain comes and goes, encouraged to give a lot of water". (P3, FGD-caregiver/patient, mother, 28 years old)*

Perceived facilitators

Almost all FGD participants (caregivers of children on HU, clinicians, and pharmacists) reported common facilitators being 1) Good compliance, 2) Improving symptoms, and 3) Active medical insurance/financial stability.

Good compliance

One of the factors which enabled clinicians to initiate HU was regular attendance as a proxy to compliance. All the care givers were adherent to hydroxyurea as per doctor's advice.

> *"Some of the factors which enable me to initiate hydroxyurea and monitor progress of the child include if the child is complying well to the drug and attends clinic regularly" (P5, FGD-clinicians, registrar)*

Improving symptoms

Caregivers continued to give HU to their children because of improving symptoms as well as reduced complications, thereby improving the quality of life.

> *"Yes, right now he has no more pain and plays well with colleagues, and I give the medicine because I see improvement in my child's condition" (P1, FGD-caregiver/patient, mother, 35 years old)*

Active medical insurance/Financial stability

Almost all FGD participants perceived that, good financial stability and working/active medical insurance were the means to acquire hydroxyurea. Pharmacists also perceived an increase in number of SCA patients being a facilitator.

> *"Some of the factors which also facilitates me to initiate hydroxyurea is that if the patient has insurance and indication of initiation" (P1, FGD-clinicians, Paediatrician)*
>
> *"I have medical insurance, every 1 month, I get the drugs" (P2, FGD-caregiver/patient, mother, 32 years old)*

Perceived barriers

Almost all FGD participants (caregivers of children not on hydroxyurea, clinicians, and pharmacists) reported common barriers being 1) Unawareness of caregivers on hydroxyurea, 2) Cost/Lack of medical insurance, 3) Availability, 4) Fear of side effects.

Unawareness of caregivers

Caregivers of children not on hydroxyurea reported frequent complications (frequent pain episodes, blood transfusion and infections) as well as lack of knowledge on hydroxyurea.

> *"Yes, he usually gets frequent severe pain and jaundice especially in the eyes, I haven't been told about hydroxyurea" (P5, FGD-caregiver/patient, older mother, 53 years old)*

Whereas clinicians also reported increasing workload and unawareness to some doctors being a barrier.

> *"Increased workload in the clinic and unawareness by other doctors is one of the barriers I face to initiate hydroxyurea, I think there is a need of increasing awareness of hydroxyurea to clinicians as well, not only the care givers." (P6, FGD-clinician, registrar)*

Cost/Lack of medical insurance

One out of the six caregivers knew that their child had to be initiated on hydroxyurea, but the barrier was high cost of the drug and lack of medical insurance.

> *"Yes, I know about hydroxyurea but hasn't been initiated because I can't afford it and my child has no medical insurance" (P3, FGD-caregiver/patient, mother, 38 years old)*

Most of the pharmacists mentioned that the drug is imported from outside the country, and the cost is around 800-1000 Tanzanian Shillings per capsule.

> *"No, it is not locally made, we usually import from India" (P1, FGD- Pharmacists, supervisor)*

Clinicians also reported those patients on medical insurance (NHIF) usually received only monthly dose of hydroxyurea, hence monthly attendance is also perceived as a barrier.

> *"Lack of money, monthly clinic attendance in case of NHIF is another barrier for care givers/patients to access hydroxyurea" (P1, FGD- clinicians, paediatrician)*

Along with cost and lack of medical insurance, pharmacists also perceived that, although the patient has medical insurance, time to acquire a special permit to access hydroxyurea is a barrier.

> *"For NHIF patients, they need special permit and takes time to get it" (P4, FGD-Pharmacists, intern)*

Availability/fear of side effects

Clinicians and pharmacist also perceived availability of hydroxyurea as well as fear of side effects being a barrier to initiate/acquire hydroxyurea.

> *"Only available as capsules, inconvenient to give and quite expensive" (P6, FGD-Pharmacists, dispensing officer)*
>
> *"Yes, another barrier is fear of side effects, especially when they are been told it's a cancer drug" (P6, FGD-clinicians, registrar)*

Discussion

The study contributes to the understanding of the coverage gap, clinical outcomes, barriers and facilitators of HU use among children with SCA attending a tertiary clinic at Muhimbili National Hospital in Dar es Salaam, Tanzania.

A total of 400 participants were included, majority were males (59%), aged less than 11 years with a median age of visiting haematology clinic being 6 years. Similar age distribution was observed in studies done elsewhere in Tanzania (17). The observed median age of diagnosis in this study was 2 years and 8 months old, only 19.8% of the children had been diagnosed less than 9 months of age. Saidi et al, 2016 showed a median age of diagnosis of 3 years and only 3.2% were diagnosed in infancy (17). In contrast, a study done in Democratic Republic of Congo, showed a higher median of age of diagnosis at 7 years (20). This signifies the need of newborn screening program to make an early diagnosis, follow ups and timely interventions. Additionally, it is key for the health care providers to be knowledgeable and continuously assess children for early diagnosis especially those missed during newborn screening.

More than half of children had at least one hospitalization in their lifetime, among the three common reasons of hospitalization were bone pain, severe anaemia, and sepsis. Hospitals in London and Paris between the year 2008 and 2012 reported similar reasons of admissions (26). Studies done in parts of Africa (Nigeria, DRC, and Tanzania) support our findings, reporting the three main reasons of admissions being painful crisis, sepsis and anaemia (16, 17, 20, 27, 28).

The coverage gap for HU among the study participants was 65%, the main barriers were caregiver unawareness, lack of health insurance/inability to afford the drug. Most of the parents/caregivers were unaware of HU which means proper guidance/education and counselling is needed. Although lack of medical insurance was a barrier to acquire HU, even with children who had active medical insurance, it was reported to be time consuming, required a special permit from health insurance company to obtain hydroxyurea, lack of money and monthly clinical attendance for a refill were additional barriers.

Reports around the world show similar barriers as found in our study. Thornburg et al 2010, assessed the barriers to HU use in 75 children with SCA at Duke University Medical Centre (29). Lack of clinic visits, transportation and lapse of insurance were some of the barriers mentioned. The study also highlighted continuous education and awareness is needed to adhere to hydroxyurea so that it improves the quality of life of children with SCA (29).

Together with the provider and patient related factors as above; Brandow et al 2010 reported poverty, lack of insurance, lack of transportation as some of the system related barriers to HU use (14, 30).

In Sub-Saharan Africa, the use of HU is also hindered by the socio-economic status. Aloni et al in 2017 assessed 108 sickle cell anaemia children with acute complications in Democratic Republic of Congo. The main barriers included cultural barriers (stigma and ignorance), lack of insurance, low socio-economic status, drug availability and high cost of the drug (20). Likewise, the study by Saidi et al in 2016 reported none of the patients received hydroxyurea due to high cost, limited availability and the ability to monitor side effects (17).

A survey among clinicians and caregivers/patients done at 13 centres in Nigeria by Chide et al in 2022 found that among the clinicians, limited knowledge of HU and low self-efficacy to prescribe as well as limited availability of the drug and additional cost of lab monitoring were some of the barriers. Care givers and patients reported lack of knowledge about HU and fear of side effects (31).

In Tanzania, there have been significant efforts to influence policy, guidelines, and process to increase HU use. In 2022, a policy brief was published discussing the same with various stakeholders (32). A publication by Ambrose et al in 2023 found that paediatric patients accessing HU via insurance and project but not cash, experienced significant improvement in clinical and haematological outcomes (16). Monitoring and evaluation towards progressive efforts is needed to close the coverage gap.

In this study 35% of children were on hydroxyurea, most of the common reasons of initiation were frequent VOC, stroke, frequent blood transfusions and ACS. Furthermore, focus group discussions with caregivers of children on HU showed that most of the caregivers were not forgetting or stopping to give HU for their children believing the drug has helped to reduce the sickle related events. This is a proxy of acceptance and need to increase initiatives to close the coverage gap of HU use.

In this study, the clinical outcomes after hydroxyurea use which were measured included the number of blood transfusions, number of hospitalizations and the proportion of sickle related events. Both the proportion of blood transfusions and hospitalizations were reduced for those who were on HU compared to those who were not on HU. Likewise, the proportion of sickle related events were lower among the HU users compared to those who were not on hydroxyurea except for bone pains, ACS and stroke. Noting that these were among the common reasons to initiate HU, it could reflect the late diagnosis, late initiation and maximum dose required to improve clinical outcomes. In the study by Ambrose et al, children have been observed to have high baseline stroke levels through transcranial Doppler (TCD) ultrasound (19). Transcranial Doppler screening plus hydroxyurea at the maximum tolerated dose is an effective stroke prevention strategy, supporting wider hydroxyurea access for patients with

sickle cell anaemia inclusive of Tanzania (18). In our study, it could be that children are using HU but not attaining the dose that could improve outcome or there are other factors affecting good outcome. In agreement to our results, similar studies reported beneficial effects of hydroxyurea in reducing sickle related events and/or complications (8, 10, 13, 33, 34).

Our study had limitations, the fact that this study was conducted at a tertiary hospital, enrolled children with SCA may have better access to medical care in general or may have a higher prevalence of SCA related events that provoked them to seek medical attention. On the same note, at least 7% of diagnosis was based on sickling test which is not the gold standard for sickle cell disease in children. This highlight areas of clinical improvement, a missed opportunity to confirm the diagnosis or could be newly referred cases to a tertiary clinic presenting with overwhelming symptoms that hindered/delayed confirmatory tests.
Respondent bias, parental education and recall bias may influence the reported presence and number of events but the use of case notes to additional information required was an added advantage. We acknowledge the omission of recording the focus group discussion and lack of an independent note taker due to budgetary limitations, but the academic involvement of the principal investigator and the sequential approach creates a unique strength and generated valuable information hard to ignore.

Conclusion

Children with SCA were diagnosed late, and coverage for HU use was low. Children are not initiated HU due to multiple barriers such as lack of awareness, lack of insurance, cost and availability of the drug. Hence, much effort is needed in increasing awareness and availability of HU in order to reduce the debilitating complications so as to improve the quality of life of children suffering from SCA.

Declarations

Ethical approval and considerations

Ethical clearance was obtained from the institutional review board of Muhimbili University of Health and Allied Sciences (MUHAS) with an approval number DA.287/298/01A. Permission to conduct the study was obtained from the Muhimbili National Hospital (MNH) administration. Confidentiality was assured and written informed consents were obtained from parents/caretakers of the child before any study procedures. Clinicians attending the patients were notified of the children who were not on hydroxyurea for possible initiation.

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Conflict of interests

The authors declare no conflict of interests regarding the publication of this paper.

Authors contributions

NSM and NSS conceptualized the study. NSM, NSS, PS and YS participated in the study design, data collection, analysis, interpretation and writing of the manuscript. LC and JM reviewed, edited and proofread the manuscript. All authors revised the manuscript and gave final approval of the version to be published.

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