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Adherence to hydroxyurea therapy and health-related quality of life in children with sickle cell anaemia at Korle Bu Teaching Hospital in Ghana

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Abstract

Background: Sickle cell anaemia (SCA) causes numerous acute and chronic complications, which can result in significant morbidity and mortality. Hydroxyurea (HU) therapy in individuals with SCA is associated with a reduction in disease severity.

Objective: The study aimed to determine the relationship between adherence to HU therapy and health-related quality of life (HRQOL) scores in children with SCA (HbSS) at Korle Bu Teaching Hospital (KBTH) and identify any barriers to HU adherence.

Methods: A cross-sectional descriptive study was conducted at the paediatric sickle cell clinic of the KBTH. One hundred and fifteen children aged $2 - 12$ years with HbSS receiving HU therapy and their primary caregivers were enrolled on this study. Demographic and HU-related data were obtained from medical records and interviews with caregivers. The 8-item Morisky Medication Adherence Scale (MMAS-8©) and haematologic response based on mean corpuscular volume (MCV) were used to assess HU adherence. Caregivers and children aged 8 - 12 years also completed the Paediatric Quality of Life Inventory (PedsQLTM) SCD-module version 3.0. For children aged $5 - 7$ years, the PedsQLTM SCD-module version 3.0 was administered by interview.

Results: Seventy-nine (68.7%) of children had high adherence to HU therapy using the MMAS-8©. The mean PedsQLTM scores were 96.9 $\pm$ 6.0 and 96.3 $\pm$ 7.2 for the child (n = 91) and caregiver (n = 114), respectively. Children with high HU adherence had significantly higher PedsQLTM scores than those with low or moderate adherence. Neither child's current MCV nor mean change in MCV correlated with child or caregiver PedsQLTM scores. The main barrier to HU adherence identified by children aged $\geq$ 8 years was forgetfulness, while the cost of HU was the main barrier to adherence reported by caregivers.

Conclusion: Children with SCA with high adherence to HU had the highest HRQOL scores using the PedsQLTM SCD-module version 3.0. Routine assessment of barriers to HU adherence can provide important information to help guide relevant interventions.

Keywords: hydroxyurea, adherence, quality of life, sickle cell anaemia, children, Ghana

INTRODUCTION

Sickle-cell disease (SCD) is a group of autosomal recessive haemoglobin disorders resulting from the inheritance of the sickle β-globin gene and production of predominantly sickle haemoglobin (HbS) or HbS in combination with other haemoglobins such as C, D, E or beta-thalassemia. Countries in sub-Saharan Africa have a disproportionately high burden of disease [1,2]. In Ghana,

1 in every 50 children is born with SCD, with the majority having sickle cell anaemia (SCA or HbSS), the most severe phenotype [3]. The pathophysiologic mechanism of SCD is complex involving HbS polymerisation, vascular occlusion, haemolysis, endothelial cell activation, hypercoagulability and nitric oxide depletion [4]. Numerous complications are associated with SCD in children, including acute painful episodes, acute chest syndrome, splenic sequestration, stroke, infections and severe anaemia. These complications may result in hospitalisations, blood transfusions, organ failure and death [5,6]. Health-related quality of life (HRQOL) is a

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multidimensional construct that assesses an individual's perception of the impact of a disease condition on physical, psychological, social and emotional functioning and well-being [7]. Several instruments have been utilised to assess HRQOL in children with chronic conditions, including generic and disease-specific measures [8]. In SCD, the lifelong nature of the condition, the need for frequent clinic visits, chronic anaemia, intercurrent pain, and other acute illnesses can be particularly burdensome. Generally, children with SCD have lower HRQOL scores across multiple domains than children without SCD, using child self-report and parent proxy reports [9–11]. Hydroxyurea (HU) is currently approved as a disease-modifying therapy in children and adults with SCA [12]. Effective disease-modifying agents substantially change the course of a disease by reducing the frequency of acute symptoms, preventing or slowing disease progression and improving quality of life. HU, a ribonucleotide reductase inhibitor, induces foetal haemoglobin (HbF) synthesis, actively inhibiting sickle polymerisation and reducing haemolysis. This causes an increase in total haemoglobin level and the mean cell volume (MCV). These changes in HbF and MCV are used to assess treatment response and are surrogate markers of HU adherence [13]. The HU also decreases white blood cell, reticulocyte and platelet counts, modifying blood cell and vascular endothelium interactions and reducing adhesion, activation, inflammation and vasoconstriction [12,14].

The benefits of HU in children with SCA include fewer episodes of pain and acute chest syndrome, decreased need for blood transfusions and hospitalisations, stroke prevention and a reduction in direct healthcare costs [14-21]. Caregivers and children on HU therapy also report higher HRQOL scores than those not on HU [22] though this may be adversely influenced by poor treatment adherence [23]. Since 2011, the Paediatric SCD clinic in Korle Bu Teaching Hospital (KBTH), Accra, has included HU therapy in managing children with SCA, initially only for patients with severe disease manifestations such as recurrent pain, hospitalisation for acute chest syndrome and stroke prevention. However, there is a paucity of local data on its impact on the child's functioning and well-being. This study aimed to assess the relationship between adherence to HU therapy and HRQOL in children with SCA at KBTH and identify any barriers to HU adherence.

MATERIALS AND METHODS

Study design and sites
This descriptive, cross-sectional study was conducted at the paediatric sickle cell clinic, KBTH, Accra. The KBTH is the largest hospital in Ghana and a major tertiary referral centre in the southern sector of the country. The paediatric sickle cell clinic is a subspecialty clinic within the Department of Child Health, KBTH. At the time of data collection in 2018, only children aged ≤ 12 years were eligible to be seen at the Department of Child Health using the National Health Insurance Scheme (NHIS).

Those older than 12 years were referred to the adult SCD clinic at the Ghana Institute of Clinical Genetics, KBTH. In the paediatric clinic, an estimated 500 children with SCA were on HU therapy for various indications. Before the start of HU, caregivers of patients received counselling on HU therapy and laboratory test requests for baseline renal function test, liver function test, and full blood count with reticulocyte count. The HbF levels were not routinely checked due to cost, as the test was only available through a few privately owned laboratories. The initial dose of HU was approximately 20.0 mg/kg/day. Monitoring of haematologic indices for toxicity and response was done through monthly full blood count with reticulocyte count and changes in MCV from baseline. Depending on the blood counts, doses of HU were either maintained or escalated by 2.5 – 5.0 mg/kg/day every 8 – 12 weeks until the patient attained a maximum therapeutic dose titrated to the absolute neutrophil count or a maximum dose of 35 mg/kg/day. Where there was evidence of haematologic toxicity HU dose was reduced to a pre-toxicity dose of up to 5 mg/kg/day below the current dose. As defined by clinic guidelines, evidence of haematologic toxicity included severe anaemia, neutropenia, thrombocytopenia or reticulocytopenia. The HU was only available at selected pharmacies in 500mg capsule formulation, which required reconstitution into a suspension for young children unable to swallow capsules. The cost of HU was not covered by the NHIS and required out-of-pocket payment by caregivers at 2.5 – 3.0 Ghana Cedis per 500 mg capsule. All children were on folic acid as part of their routine SCD medications.

Study population and sampling
Inclusion criteria were children diagnosed with HbSS, aged 2 –12 years, on HU therapy, and attending the paediatric sickle cell clinic at KBTH with their primary caregivers. The selected children must have been on HU for at least one year to allow enough time for titration to the maximum tolerated dose. Children on concurrent ('bridging') blood transfusions were excluded. From the clinic register, about 40 patients on HU attended the clinic each month. A purposive sampling technique was used to select eligible participants who had been on HU for at least one year and would be available during the study period from June through August 2018. Caregivers were contacted by telephone and informed about the study. Those who were willing to participate were given a scheduled clinic appointment during which written informed consent and assent, if a child was age ≥ 8 years, was obtained.

Data collection
Demographic information and data on HU therapy were obtained from medical records as well as interviews with caregivers and children aged 8 – 12 years. Adherence to HU therapy was determined using the 8-item Morisky Medication Adherence Scale (MMAS-8©) [16] with a least obtainable score of 0 and the maximum obtainable score of 8.0. The Scale includes seven yes/no questions and one

multiple-choice question where the best option is chosen. The words "medicine" and "medication" were replaced with "hydroxyurea". Based on the MMAS-8©, adherence was categorized as low (score, < 6), medium (score, ≥ 6 to < 8) or high (score, = 8) [24-26]. Additionally, adherence was inferred from the haematologic response, using baseline pre-HU and most recent MCV values. The Paediatric Quality of Life Inventory (PedsQLTM) SCD-module version 3.0 [11-13] was used to determine the HRQOL of study participants. The PedsQLTM SCD-module version 3.0 was developed and validated specifically for children with SCD to improve their understanding of their health and well-being and assess the benefits of any interventions or disease-modifying treatments [27,28]. The 43-item instrument comprises nine dimensions — including pain and hurt, pain impact, pain management and control, worry, emotions, treatment, and communication — assessed during the previous four weeks. Age-specific child report forms were used for children aged 5 – 7 years and 8 – 12 years. Parent-proxy report forms were utilised for children aged 2– 12 years to assess the caregiver's perception of the child's HRQOL [27]. Forms were self-completed by parents and children aged 8 – 12 years. For children aged 5 – 7 years, the forms were interviewer-administered. The interviewer read out each question, and the child pointed to the picture of a facial expression that corresponded with their response. Initial scoring was on a 5-point Likert scale from 0 (never a problem) to 4 (almost always a problem). To compute the actual PedsQLTM score, the responses were reverse-scored with the linear transformation of 0 – 4 scale to 0 – 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). The mean PedsQLTM score was calculated using the sum of the items divided by the number of items answered [27]. The maximum obtainable mean score was 100. The higher the mean score, the better the HRQOL. For instance, scores of 81 or higher on the PedsQLTM pain scales are indicative of good HRQOL [29].

Data analysis

Data were cross-checked for accuracy and completeness and analysed with the Statistical Package for Social Sciences version 21 for Windows (Armonk, New York, USA: IBM Corporations). Summary statistics including percentages, proportions, and mean (± standard deviation) were used to summarise key variables of the study such as socio-demographic characteristics of participants, HU data for children, adherence to HU, and MCV. Pearson's Correlation was used to find associations between MCV and PedsQLTM SCD-module version 3.0 score. The level of statistical significance was $p < 0.05$.

RESULTS

Of 125 caregivers who initially agreed to participate in the study, five did not show up for the scheduled clinic appointment, and five declined participation at the time of data collection. Hence, 115 children with SCA and their caregivers finally participated in the study. The mean age of the children aged 4 – 12 years was 8.7 ± 2.7 years.
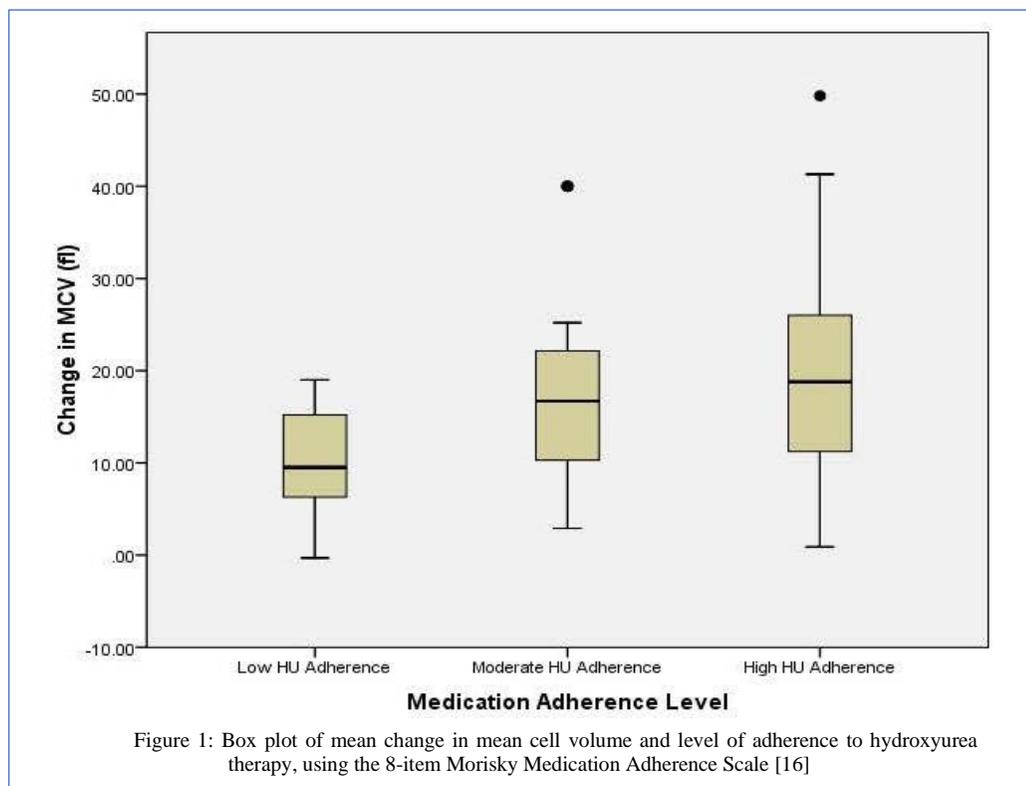

Figure 1: Box plot of mean change in mean cell volume and level of adherence to hydroxyurea therapy, using the 8-item Morisky Medication Adherence Scale [16]

Table 1. Participants' scores based on an assessment by the Paediatric Quality of Life Inventory (PedsQLTM) SCD-module version 3.0

Parameter	Number	Mean	Median	SD	Range
PedsQLTM for child	91	96.9	100.0	6.0	61.6 –100.0
PedsQLTM for caregiver	114	96.3	98.9	7.2	56.4– 100.0

SD, standard deviation

About 53% (n = 61/115) of the children were male. The clinical indications for initiating HU therapy were primary stroke prevention (49.6%, n = 57), frequent painful episodes (17.4%, n = 20), secondary stroke prevention (13.0%, n = 15), acute chest syndrome (11.3%, n = 13), frequent transfusions (7.8%, n = 9), and others (0.9%, n = 1). The mean dose of HU was 22.7 ± 3.8 mg/kg/day (range, 15.3 – 33.7 mg/kg/day) and the mean duration of HU therapy was 2.8 ± 1.1 years) (range, 1.0 – 7.0 years). Most (n = 103, 89.6%) participants did not report any of the listed side effects (abdominal pain, nausea, vomiting, headache and skin hyperpigmentation) of HU. The mean MMAS-8© score for all 115 children was 7.52 ± 0.87 (range, 4.0 – 8.0). Overall, 68.7% (n = 79) of the children in the study had high adherence to HU therapy, 23.5% (n = 27) had moderate adherence, and 7.8% (n = 9) had low adherence.

All children (100%, n = 8) aged 2 – 4 years had high adherence. Among children aged 5 – 7 years, 75.8% (n = 25/33) had high adherence, while 62.2% (n = 46/74) of the children aged 8 – 12 years had high adherence. None of the children aged 2 – 4 years and 5 –7 years had low adherence. In comparison, 12.2% (n = 9/74) of the children aged 8 –12 years had low adherence. The mean baseline MCV and mean current MCV for the children were 83.5 ± 6.3 femtoliters (fL) and 101.6 ± 9.4 fL, respectively. The mean change in MCV levels was 18.2 ± 9.9 fL. Almost all (94.7%, n = 109/115) participants had
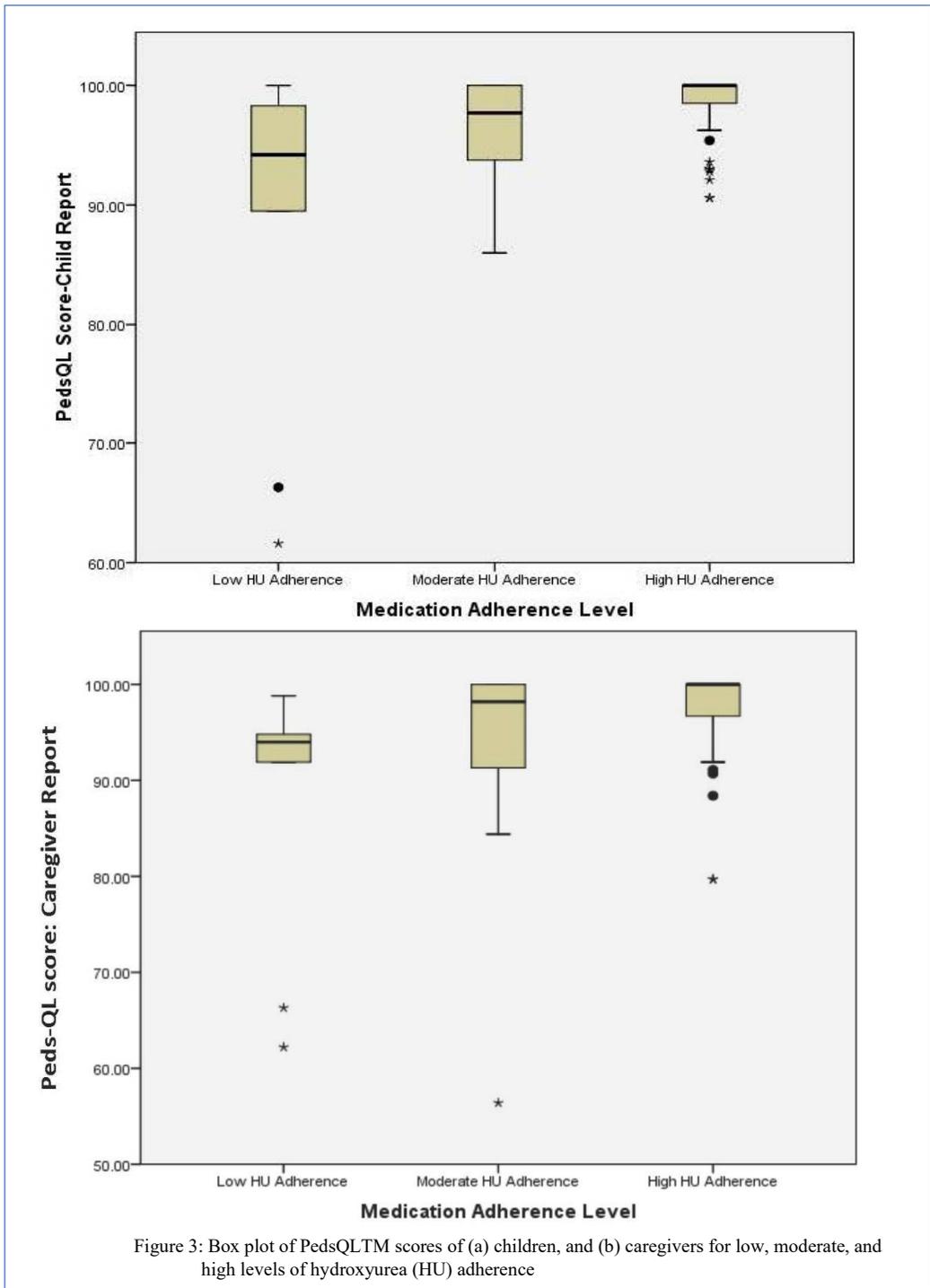
an increase in MCV from baseline. Figure 1 is a box plot showing the mean change in MCV based on the level of adherence assessed with the MMAS-8©. A total of 91 children completed the PedsQLTM child self-report, and 114 caregivers completed the caregiver-proxy report, as shown in Table 1. One caregiver's report was excluded due to incomplete responses. Based on Pearson's correlation analysis, there was a significant positive correlation between the child PedsQLTM and caregiver PedsQLTM scores (r = 0.644, $p < 0.001$). The MMAS-8© and PedsQLTM child and caregiver scores were also positively correlated (Table 2). Figures 2 and 3 are box plots showing the PedsQLTM child and caregiver scores, respectively, for children with low, moderate and high levels of adherence. For both child and caregiver reports, the PedsQLTM scores were highest for those with high adherence ($p = 0.002$ and $p = 0.001$, respectively).

Current MCV and mean change in MCV did not correlate with the PedsQLTM scores for both child and caregiver reports (Table 2). Using the overall median current MCV value of 100.5 fL to categorise participants into low current MCV and high current MCV, there was no significant difference in the PedsQLTM scores between the two groups for the child ($p = 0.633$) and caregiver ($p = 0.287$). There were, however, positive correlations between the MMAS-8© score and the mean change in MCV (r = 242, $p = 0.009$) as well as the current MCV (r = 214, $p = 0.022$). Among children ages 8 – 12 years, 73 out of 74 responded to the question about barriers to HU adherence. Of the 73, 69.9% (n = 51) reported having no barriers to adherence, 28.8% (n =21) reported forgetfulness as a barrier to adherence, and 1.4% (n = 1) identified the HU regimen as a barrier to adherence. Of 115 caregivers enrolled on this study, 32.2% (n = 37) indicated no barriers to HU adherence. Of the remaining 78, the commonest barrier was medication cost (89.7%, n = 70/78). Other barriers included forgetfulness (9.0%, n = 7/78) and competing daily activities (1.3%, n = 1/78).

Table 2. Correlation between MMAS-8©, mean cell volume, and PedsQLTM scores

Parameters	Statistics	Current MCV in fL	Change in MCV in fL	MMAS-8©	PedsQLTM score for child	PedsQLTM Score for caregiver
Current MCV in fL	r	1				
	p value					
Change in MCV in fL	r	0.787	1			
	p value	0.000*				
MMAS-8©	r	0.214	0.242	1		
	p value	0.022*	0.009*			
PedsQLTM score for child	r	0.126	-0.036	0.408	1	
	p value	0.235	0.733	0.000*		
PedsQLTM score for caregiver	r	0.101	-0.113	0.297	0.644	1
	p value	0.285	0.231	0.001*	0.000*	

MMAS-8©, 8-item Morisky Medication Adherence Scale; r, Pearson's correlation coefficient PedsQLTM, Paediatric Quality of Life Inventory SCD-module version 3.0; MCV, mean cell volume, fL, femtolitres; *, p value < 0.05 is statistically significant

Figure 3: Box plot of PedsQLTM scores of (a) children, and (b) caregivers for low, moderate, and high levels of hydroxyurea (HU) adherence

DISCUSSION

Recently published clinical trials have demonstrated the efficacy and safety of HU in children with SCA in sub-Saharan Africa [30-32]. Current recommendations are for HU is to be offered to every individual with SCA, irrespective of severity [33,34], meaning that the use of this therapy will increase several-fold, particularly in sub-Saharan Africa, which has the greatest burden of disease. The chronic course of SCD plus acute manifestations of illness can hurt the quality of life, especially in those with HbSS and HbSβo, who generally have a more severe disease [35]. The use of disease-modifying therapies like HU has been shown to significantly increase HRQOL and physical functioning [22,23], which is likely because HU reduces painful episodes and increases haemoglobin

levels, decreasing fatigue and improving energy levels. Additionally, there are fewer acute care hospital visits and admissions, which minimises disruptions to daily life. In the present study, all patients had severe disease (HbSS) with previous clinical complications or were at increased risk of stroke. Despite this, the mean PedsQLTM scores for both child and parent reports were indicative of high HRQOL. Although this study did not explore the objective impact of HU on the clinical outcomes of participants, the high PedsQLTM scores represent high levels of well-being from the patient/caregiver's perspective [29]. HRQOL is an important patient-reported outcome. It is a reliable, valid, and population-specific method of determining HRQOL that should be incorporated into practice and clinical trials of interventions for chronic diseases to assess the efficacy of treatment from patients' points of view.

A limitation of our study is the unavailability of PedsQLTM scores before HU initiation within our patient cohort or in an HU-naïve population within the same clinic for comparison. This can be the focus of the future, and a prospective study would need to be designed with appropriate consideration to the issue of response shift over time [7]. The laboratory effects of HU include increased HbF and MCV. MCV is an inexpensive substitute for HbF in measuring haematologic response and adherence during HU therapy [36]. In the present study, almost all participants showed an increase in MCV from baseline, indicating an HU treatment response. Although both current MCV and mean change in MCV showed a positive correlation with the MMAS-8$^©$, there was no correlation between the MCV and PedsQLTM scores. Due to variability amongst patients, it is unclear what percentage change in MCV definitively correlates with high medication adherence. However, the high PedsQLTM scores in study participants, irrespective of change in MCV, suggest some benefit of HU once there is evidence of laboratory response. Measures of HU adherence used across studies are varied. This study used the MMAS-8$^©$ scale, with about two-thirds (68.7%) of children having high adherence. HU adherence in multicentre clinical trials was 74 – 94% using two weekly pill counts and medication event monitoring system caps. However, in clinical practice, without the rigours of a drug trial, adherence rates are much lower and consistent with the current findings [37,38].

This study showed a significant correlation between the MMAS-8$^©$ and the PedsQLTM score. Children with high HU adherence had the highest PedsQLTM scores. Non-adherence can nullify any potential benefits of HU and may lead to disease complications and potentially reduced HRQOL. Many factors can influence HU adherence, and awareness of patients' perceptions and unique circumstances is critical to overcoming adherence barriers [23]. The cost of HU was the major barrier identified by caregivers in the present study, as the NHIS does not cover it. In November 2019, to improve HU accessibility and affordability, the Sickle Cell Foundation of Ghana, in collaboration with Novartis and the Government of Ghana, launched the "Ahodwo" Programme, which provides HU at no cost to patients in selected health facilities across the country [39]. This initiative will also eventually include the cost of laboratory tests required for HU monitoring. The Programme has also advocated for the inclusion of HU as an essential medicine which can be offered under the NHIS. Once the cost barrier is removed, it will be even more important to regularly monitor HU adherence to determine if there are any additional obstacles to adherence, such as long-term effects of HU, high frequency and length of clinic visits, and ease of obtaining refills and other access barriers [22,23].

For the 73 children aged 8 – 12 years who were interviewed in this study, the commonest barrier was forgetfulness. Notably, this age group was the only category with participants who had low adherence to the MMAS-8$^©$. Low HU adherence was reported in 33% of adolescents with SCD (age 11 − <15 years) in Riyadh, Saudi Arabia and almost three-quarters (74%) of adolescents and young adults in the United States, using the MMAS-8$^©$ or a modified version [23,40]. As children grow older and become more independent, parental involvement in medication-taking reduces or may even be actively resisted, with the risk of lower adherence without parental supervision [40]. Medication reminder strategies such as keeping the medication visible, using a calendar or the alarm function on mobile phones can be employed in homes to reduce forgetfulness [14]. This should be included in the counselling sessions between healthcare providers, caregivers and older children before HU initiation and during follow-up visits.

Conclusion
In children with SCA at KBTH, adherence to HU therapy using the MMAS-8$^©$ was positively correlated with HRQOL scores. Routine assessment of adherence and barriers to HU adherence, particularly in older children, can provide important information which would help guide relevant interventions for this patient population.

DECLARATIONS

Availability of data

Data is available upon request to the corresponding author.

REFERENCES

1. Alkanhal H, Bakrman A, Alzahrani A, Alotaibi M, Bin SA, AlHejjei S (2014) Adherence to Hydroxyurea Therapy in Patients with Sickle Cell Disease at King Khalid University Hospital in Riyadh. J Blood Disord Transfus 05: https://doi.org/10.4172/2155-9864.1000242

2. Walsh K, Cutrona S, Kavanagh P, Crosby L, Malone C, Lobner K (2014) Medication adherence among pediatric patients with sickle cell disease: a systematic review. Pediatrics 134:1175–1183

3. Candrilli S, O'Brien S, Ware R, Nahata M, Seiber E, Balkrishnan R (2011) Hydroxyurea adherence and associated outcomes among Medicaid enrollees with sickle cell disease. Am J Hematol 86:273–277

4. Quieroz A, de Castro LC, do Nascimento E, de Braganca PB, Bonini-Domingos C, Cardoso G (2013) The Mean Corpuscular Volume and Hydroxyurea in Brazilian Patients with Sickle Cell Anemia: A Surrogate Marker of Compliance. J Blood Disord Transfus 4:157. https://doi.org/10.4172/2155-9864.1000157

5. Dampier C, Lieff S, LeBeau P, Rhee S, McMurray M, Rogers Z (2010) Health-related quality of life in children with sickle cell disease: a report from the Comprehensive Sickle Cell Centers Clinical Trial Consortium. . Pediatr Blood Cancer 55:485–494

6. Yawn B, Buchanan G, Afenyi-Annan A, Ballas S, Hassell K, James A (2014) Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA 312:1033–1048

7. Qureshi A, Kaya B, Pancham S, Keenan R, Anderson J, Akanni M (2018) Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. Br J Haematol 18:460–475

8. Opoka R, Ndugwa C, Latham T, Lane A, Hume H, Kasirye P (2017) Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a trial for children with sickle cell anaemia. Blood 130:2585–2593

9. Tshilolo L, Tomlinson G, Williams T, Santos B, Olupot-Olupot P, Lane A (2019) Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med 380:121–131

10. John C, Opoka R, Latham T, Hume H, Nabaggala C, Kasirye P (2020) Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med 38:2524–2533

11. Beverung L, Varni J, Panepinto J (2015) Clinically meaningful interpretation of pediatric health-related quality of life in sickle cell disease. J Pediatr Hematol Oncol 37:128–133

12. Panepinto J, Torres S, Varni J (2012) Development of the PedsQLTM Sickle Cell Disease Module items: qualitative methods. Qual Life Res 21:341–357

13. Panepinto J, Torres S, Bendo C, McCavit T, Dinu B, Sherman-Bien S (2013) PedsQLTM sickle cell disease module: feasibility, reliability, and validity. Pediatr Blood Cancer 60:1338–1344

14. Berlowitz D, Foy C, Kazis L, Bolin L, Conroy M, Fitzpatrick P (2017) Effect of intensive blood-pressure treatment on patient-reported outcomes. N Engl J Med 377:733–744

15. Bress B, Bellows B, King J, Hess R, Beddhu S, Zhang Z (2017) Cost-effectiveness of intensive vs. standard blood-pressure control. N Engl J Med 377:745–755

16. Morisky D, Ang A, Krousel-Wood M, Ward H (2008) Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens 10:348–355

17. Badawy S, Thompson A, Lai J-S, Penedo F, Rychlik K, Liem R (2017) Adherence to hydroxyurea, health-related quality of life domains, and patients' perceptions of sickle cell disease and hydroxyurea: a cross-sectional study in adolescents and young adults. Health Qual Life Outcomes 15:136

18. Thornburg C, Calatroni A, Panepinto J (2011) Differences in health-related quality of life in children with sickle cell disease receiving hydroxyurea. J Pediatr Hematol Oncol 33:251–254

19. Ware R, Davis B, Schultz W, Brown R, Aygun B, Sarnaik S (2016) Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet Lond Engl 387:661–670

20. Thornburg C, Files B, Luo Z, Miller S, Kalpatthi R, Iyer R (2012) Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood 120:4304–4310

21. Wang W, Oyeku S, Luo Z, Boulet S, Miller S, Casella J (2013) Hydroxyurea is associated with lower costs of care of young children with sickle cell anemia. . Pediatrics 132:677–683

22. Wang W, Ware R, Miller S, Iyer R, Casella J, Minniti C (2011) Hydroxycarbamide in very young children with

sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet Lond Engl 377:1663–1672

23. Wang W, Dwan K (2013) Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease. Cochrane Database Syst Rev 11:

24. Kassim A, Galadanci N, Pruthi S, DeBaun M (2015) How I treat and manage strokes in sickle cell disease. Blood 125:3401–3410

25. McGann P, Ware R (2015) Hydroxyurea therapy for sickle cell anaemia. Expert Opin Drug Saf 14:1749–1758

26. Strouse J, Heeney M (2012) Hydroxyurea for the treatment of sickle cell disease: efficacy, barriers, toxicity, and management in children. Pediatr Blood Cancer 59:365–371

27. Brandow A, Panepinto J (2011) Monitoring toxicity, impact, and adherence of hydroxyurea in children with sickle cell disease. Am J Hematol 86:804–806

28. Carden MA, Little J (2019) Emerging disease-modifying therapies for sickle cell disease. . Haematologica 104:1710–1719

29. Menezes A de O da P, Len C, Hilário M, Terreri M, Braga J (2013) Quality of life in patients with sickle cell disease. Rev Paul Pediatr 31:24–29

30. Dale J, Cochran C, Roy L, Jernigan E, Buchanan G (2011) Health-related quality of life in children and adolescents with sickle cell disease. J Pediatr Health Care 25:208–215

31. Palermo T, Schwartz L, Drotar D, McGowan K (2002) Parental report of health-related quality of life in children with sickle cell disease. J Behav Med 25:269–283

32. Eiser C, Morse R (2001) The measurement of quality of life in children: past and future perspectives. J Dev Behav Pediatr 22:248–256

33. Megari K (2013) Quality of Life in Chronic Disease Patients. Health Psychol Res 1:27

34. Ware RE de MMTLAM (2017) Sickle cell disease. Lancet Lond Engl 390:311–312

35. Makani J, Ofori-Acquah S, Nnodu O, Wonkam A, Ohene-Frempong K (2013) Sickle cell disease: new opportunities and challenges in Africa. Scientific World Journal 193–252

36. Kapoor S LJPL, Little J, Pecker L (2018) Advances in the Treatment of Sickle Cell Disease. Mayo Clin Proc 93:1810–1824

37. Ohene-Frempong K, Oduro J, Tetteh H, Nkrumah F (2008) creening newborns for sickle cell disease in Ghana. Pediatrics 121 Suppl 2:120.2-121

38. Grosse S, Odame I, Atrash H, Amendah D, Piel F, Williams T (2011) Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med 6 Suppl 4:398–405

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