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A RETROSPECTIVE QUASI-EXPERIMENTAL STUDY TO DETERMINE THE IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA
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A RETROSPECTIVE QUASI-EXPERIMENTAL STUDY TO DETERMINE THE IMPACT OF HYDROXYUREA ON FREQUENCY OF BLOOD TRANSFUSION IN CHILDREN WITH SICKLE CELL ANAEMIA

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ABSTRACT

Objective: **To determine the impact of and adherence to hydroxyurea use over a 6-month period on the frequency of blood transfusion among children (1-18 years) with sickle cell disease (SCD).**

Study design, setting and duration: **A retrospective quasi-experimental study conducted in a public (Kenyatta National Hospital) and a private (Gertrude's Garden Children Hospital) hospital setting in Kenya from February to May 2017.**

Subjects: **Participants were children aged 1-18 years with a diagnosis of sickle cell anaemia confirmed by serum electrophoresis who had been on hydroxyurea treatment for at least 6 months.**

Interventions and outcomes: **The main intervention and outcome measures were hydroxyurea treatment and frequency of blood transfusion respectively.**

Results: **A total of 64 children were studied. The mean age was 7.6 years (SD ±3.7). The mean decrease in the number of blood transfusions during the 6–12-month period after adequate use of hydroxyurea was 0.9 (95% CI 0.7 - 1.2; $p < 0.001$). Majority of the participants received hydroxyurea dosages of < 20mg/kg/day (51/64; 79.7%), took hydroxyurea as per the prescription (50/64; 78.1%), and didn't experience any side effects (56/64; 87.5%).**

Conclusion: **This study suggests that hydroxyurea significantly reduces the frequency of blood transfusions in children aged 1-18 years with minimal side-effects.**

INTRODUCTION

Sickle cell disease (SCD) presents a large burden of disease in in sub-Saharan Africa (sSA). The World Health Organization (WHO) has declared sickle cell anaemia (SCA) a public health priority. There are 300,000 children born with SCA annually [1], with approximately 75% of these of these births occurring in sSA. It is estimated that 50–80% of these patients will die before adulthood [2]. In 2013, there were 176,000 deaths due to SCD up from 113,000 deaths in 1990. Individuals afflicted by SCD often develop sickle cell crises generally grouped as: Acute vascular occlusion (painful crisis), acute chest syndrome (ACS), aplastic crises, haemolytic crises and splenic sequestration crisis. Haemoglobin electrophoresis is used in the diagnosis of SCA [3]. It is a technique which can differentiate and quantitate different types of haemoglobin.

Red blood cell transfusion may be used to treat acute complications of SCD and to prevent chronic complications. Episodic transfusions are often done in instances of acute splenic sequestration, aplastic crisis and hyperhemolysis [4], whilst chronic transfusion therapy are offered for primary stroke prevention, prevention of recurrence of stroke and pulmonary hypertension [5].

Children with SCD often undergo several episodes of blood transfusion which pose inherent risks to them [6]. Blood transfusion in all recipients, have a potential risk of causing adverse effects including infections, iron overload, allergic reactions, alloimmunization, acute or delayed haemolytic transfusion reactions (DHTRs) [7].

Globally, approximately 80 million units of blood are donated each year [8]. Of this total, 2 million units are donated in sSA, where the need for blood transfusions is comparatively higher because of maternal morbidity, malnutrition, and a heavy burden of infectious diseases such as malaria. There is chronic shortage of safe blood and blood products particularly in low- and medium-income countries (LMICs) [9]. Blood safety remains an issue of major concern in transfusion practice in most countries in sSA where national blood transfusion services and policies, appropriate infrastructure, trained personnel, and financial resources are inadequate to support the running of a voluntary, non-remunerated donor transfusion service [10].

In 1995, hydroxyurea (HU), then a new therapeutic agent, was proclaimed as a major breakthrough in the management of SCD after a number of key observations about the role of Haemoglobin F (HbF) where made [11]. The initial clinical trials of HU in SCD were stopped early after clear benefits were demonstrated in the treatment arm and the drug was rapidly licensed in the USA for the treatment of patients with severe SCD. Since then, HU has been used successfully in a variety of situations in SCD, including in very young children [12]. However, there are outstanding concerns about its efficacy and safety in the long term. The current recommendation guideline is to offer HU to infants from the age of 9 months, children, and adolescents with SCA, regardless of clinical severity to reduce the occurrence of SCD-related complications such as pain, dactylitis, ACS, anaemia etc [4].

A retrospective, single institution, cohort study of 152 patients suffering from Philadelphia-negative myeloproliferative disorders (MPD) with thrombocytosis (median follow-up 8.13 years) who were on HU therapy was done in USA to determine its toxicity and side effects. Adverse side-effects (five symptomatic macrocytic anaemia, two fever reactions, two allergic reactions, four cases each of leg painful ulcers and three acute leukemia or myelodysplasia) caused withdrawal of therapy in 16 patients [13]. The major side effect of HU is myelotoxicity, which is reversible upon discontinuation of the drug. However, HU is

significantly underutilized in patients with SCD. In 2010, Patel *et al*., conducted a 1-year retrospective cohort analysis of 93 children on HU for SCD and demonstrated that the average refill prescription rate was 58.4% implying the patients were only partially adherent to HU and thus did not receive the full benefits of the medication [14]. The barriers to HU treatment can be grouped into four categories: patient, provider, caregiver and healthcare system. The National Institutes of Health (NIH) consensus states that there have been no interventions performed to address such barriers [15].

Despite its use in high income countries for the management of SCD in children, HU is not used in this age group in LMICs including Kenya. In the Kenyan clinical guidelines HU is only recommended for adults with SCD yet many SCD related deaths occur in early childhood^.

This study therefore aims to determine the impact of and adherence to hydroxyurea use over a 6-month period on the frequency of blood transfusion among children (1-18 years) with sickle cell disease (SCD) as well as explore contextual issues that may influence recommendation for use of HU among children with SCD in LMIC settings.

MATERIALS AND METHODOLOGY

Study Design: In this study a retrospective quasi-experimental (single interrupted time series) design was employed to examine the frequency of blood transfusions in the period before initiating hydroxyurea in comparison to the frequency in the period after its introduction. Participants retrospectively completed questionnaires on the number of blood transfusions they had at a particular time point with the aid of medical reports. The time series design sets to investigate whether a change in frequency of blood transfusion occurred between two time points with a treatment intervention (HU) occurring between the two time points.

In our study our first time point was the 1-year period when the children with SCA had not initiated HU therapy, as shown in Figure 1 below.

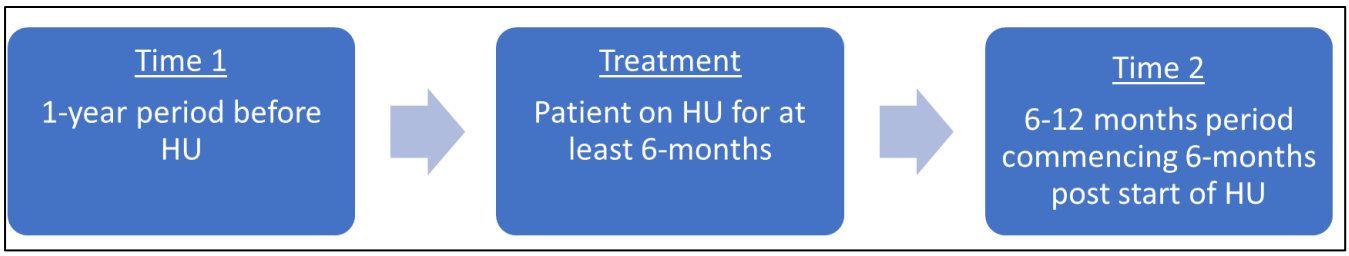

Figure 1: Schema showing the time points evaluated in the study

Study sites: The study took place in two hospitals in Nairobi that not only provide a pool of patients on management for sickle cell anaemia but more importantly the use of hydroxyurea by these patients.

The two hospitals were:

1. Kenyatta National Hospital, KNH (a public hospital).
2. Gertrude's Garden Children Hospital (a private hospital).

Ethics: The Kenyatta National Hospital-University of Nairobi Ethics and Research committee provided approval for the study (Approval reference number P633/09/2016; 24th January 2017).

Study population: The participant population consisted of male and female patients at both study sites who were evaluated to determine eligibility based on the inclusion/ exclusion criteria listed below:

Inclusion criteria: Children aged 1-18 years who have consented with a diagnosis of sickle cell anaemia (typically HbSS) confirmed by serum electrophoresis and who are on hydroxyurea, irrespective of dosage, for at least 6 months and are on follow up in the haematology clinics in KNH and Gertrude's hospital.

Exclusion criteria: Those with pre-existing severe haematological conditions like myelodysplastic disorders and human immunodeficiency virus (HIV) infection confirmed by bone marrow aspirate and rapid antibody tests respectively.

Patient recruitment: Convenience sampling was used to recruit participants at the respective haematology clinics with the aid of the multi-disciplinary healthcare team at the clinics consisting of consultants, registrars and nurses.

Sample Size: The sample size required (N=63) was calculated by the sample size equation by Corty EW and Corty RW (2011) which is useful for estimating sample sizes for correlations with pre-specified confidence intervals [16]:

$N=15.37/(\ln(B))^2+3$

Where $B= \sqrt{(1+r+w)(1-r+w)}/\sqrt{(1-r-w)(1+r-w)}$

Whereby: *r* is the sample correlation coefficient of 0.5 (predetermined by the investigator as use of HU in patients with SCA has been shown to have a correlation with a reduction of blood transfusions in previous studies [4, 11, 12, 17, 18]. An *r* value of 0.5 signifying a moderate correlation between the variables, was then chosen based on the work of Moinester and Gottfried, 2014^^); w is the significance level =0.05

Data Collection: Data were collected using questionnaires capturing; categorical variables such as; age, gender, weight, residence, use of concurrent medication, adherence and HU dose. The independent variables were time before and after initiation of HU while the dependent variables were the number of admissions and number of transfusions.

Data Analysis: The data were analysed using Stata version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Categorical variables were presented using counts and percentages. Continuous data were presented descriptively using means (standard deviations) and medians (interquartile range) as appropriate. Bivariate analyses were done using chi squares for categorical variables and also paired t-tests for the comparison of the means before and after initiation of hydroxyurea. A statistical comparison of time trends before and after the intervention was done. A Poisson regression analysis of the transfusion and admission counts while accounting for time periods was done to explore for any association between use of hydroxyurea (intervention) and frequency of blood transfusions and admissions. The results presented as Incidence Rate Ratios (IRR) with their respective 95% confidence intervals. Predicted transfusion data were presented graphically on a box plot to depict the change in the number of transfusions after the intervention. The alpha level was 5% with p values less than 0.05 considered statistically significant for all the tests.

RESULTS

A total of 64 children were recruited in the study, majority of whom were male 37 (57.8%). The mean age at admission was 7.6 years (SD= 3.7). The median age at diagnosis of SCA was 2.2 years (IQR= 0.7-3.5). Mean age when respondents started using HU was 4.8 years (SD=2.6), with median duration of use at 2.1 years (IQR=1.3-4). All the respondents agreed to being admitted due to SCA complications and the median age at the first episode was 2 years (IQR=1-4). Majority of the respondents had received blood transfusion 57(89.1%) with a median age of 2 years (IQR=0.6-4) at the first transfusion.

The median number of times a respondent had been admitted to hospitals due to SCA related complications before the use of HU was twice (IQR=1-3). Before the onset of HU use, the median number of times a patient had been admitted in the last one year was once (IQR=1-2). In the immediate 6-12 months period after continuous use of HU for at least 6 months, the median number of times a patient had been admitted was zero (IQR=0-0.2). After onset of HU use, the median number of times a patient had been admitted due to SCA complications was zero (IQR=0-1.2).

With respect to transfusion, the total number of transfusions decreased from a mean of 2.1 (95% CI 1.5-2.8) before HU to a mean of 0.7 (95% CI 0.4 - 1.1) after HU (mean decrease, 1.4; 95% CI 0.9-1.9; p <0.001) as shown in Figure 2 below.

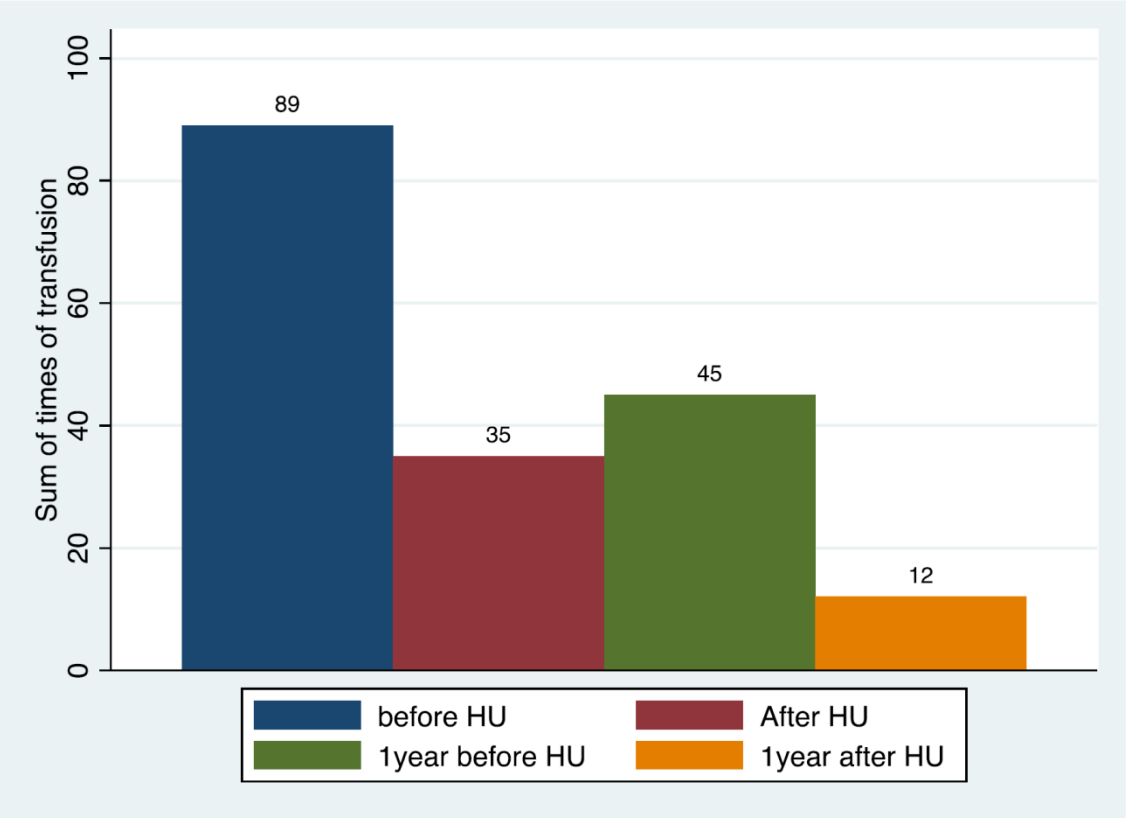

Figure 2: Histogram showing number of transfusions before and after use of hydroxyurea for 6 months

In the period 6-12 months after HU treatment, the number of transfusions decreased from a mean of 1.2 (95% CI 0.9-1.4) to 0.2 (95% CI 0.1 - 0.4) corresponding to a mean decrease of 0.9 (95% CI 0.7 - 1.2; p <0.001). Table 2 below shows a comparison of the transfusion frequency before and after HU treatment.

Table 2

Comparison of frequencies of transfusions before and after HU

Transfusion (N=64)	Mean (95% CI)	Paired t-test on difference
Number of transfusion before HU	2.1 (1.5 - 2.8)	
Number of transfusion after HU	0.7 (0.4 - 1.1)	
Difference	1.4 (0.9 - 1.9)	P value <0.001
Number of transfusion 1year before HU	1.2 (0.9 - 1.4)	
Number of transfusion 6 months - 1year after HU	0.2 (0.1 - 0.4)	
Difference	0.9 (0.7 - 1.2)	P value <0.001

The total person-years before HU was 306.7, with an incident rate of transfusion events of 44.02 per 100 person-years before the use HU. The total person-years after HU was 181.5, with an incident rate of transfusion events of 25.34 per 100 person-years after the use of HU.

The children had a statistically significant lower rate of transfusion post HU treatment compared to the period before HU treatment as shown in Figure 3 below; IRR = 0.18 (95% CI 0.09 - 0.35; $p<0.05$).

Overall, the rate of transfusion seems to increase slightly for each unit increase in the time points while holding intervention constant, IRR = 1.38 (95% CI 1.02 - 1.86).

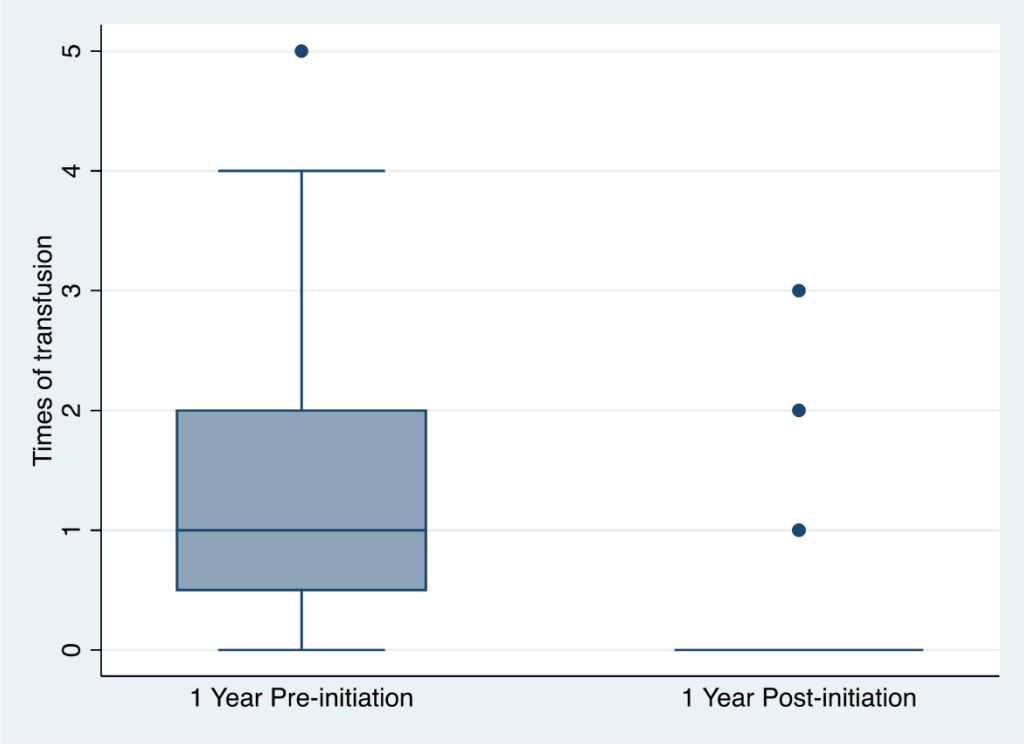

Figure 3: Box plot showing change in the number of transfusions after 6 months of HU

A greater proportion of the patients were under the capsule formulation of HU 53 (82.8%) and on alternate day dosing 37 (57.8%). The median dosage of HU was 14.5 mg/kg/day (IQR = 11.3-19). Table 3 below shows the dosing classification whereby we found majority of the children (79.7%) were under-dosed.

Table 3

Dosage classification of HU used by the participants

Dosage Classification	N (%)
Under dose '<20 mg/kg/day'	51 (79.7)
Required '20-35 mg/kg/day'	13 (20.3)

Of the 51 patients who had underdosed HU, 9 (17.6%) had received more than two transfusions compared to 42 (82.4%) who had less than two transfusions (p=0.847). The number of children who were under-dosed was also significantly higher among those who were on alternate day dosing compared to those not on alternate day dosing; 37 (72.5%) vs. 14 (27.5%) (p=0.001).

A greater number of the children take HU as prescribed 50 (78.1%). Some of the reasons for not taking HU as prescribed were: high cost and lack of availability/ forgetting to buy drugs 6(9.4%), no prescription during industrial strikes by healthcare personnel 1(1.6%), patient was advised that HU use was not to be stopped 1(1.6%) and other factors 8 (12.5%). Majority of the children had not experienced any side effect experience with the use of HU 56 (87.5%), however, for the few who had, nausea and vomiting 4(6.2%) were the most commonly reported side effect. Other reported side effects included diarrhoea, abdominal pains, alopecia, change

in nail colour, and coughing (1/64; 1.6% for each).

Besides HU, all of the children were using folic acid and penicillin V. Other prescribed drugs were Ranferon/vitamin C 8 (12.5%), Neurobion 2 (3.1%) and antimalarial drugs 2 (3.1%).

DISCUSSION

In this study we found a significant reduction in the frequency of blood transfusion in the 6-12 months period following 6 months of hydroxyurea treatment among children with SCD. A similar observation was made by Charache et al 1995 whereby there were fewer incidences of blood transfusion among adults receiving HU compared to a placebo group (48 vs 73; p=0.001) [11]. In our study this decrease remained significant whether the entire 12-month post-HU period or just the 6-month period was considered.

Wang et al (BABY HUG) in 2011, also demonstrated a similar outcome with a decrease in transfusion incidences between patients who were on HU in comparison to those who were on placebo [12]. In this study, done on babies aged 9-18 months, 35 events of transfusions were recorded in 20 patients in the HU group against 63 transfusion events in 33 patients in the placebo group [12].

As previously noted, the intervention compared to pre-intervention, holding the time points constant, the children had a statistically significant lower rate of transfusion IRR = 0.18 (95% CI 0.09 - 0.35). This result is both clinically meaningful and statistically significant. HU therefore should be encouraged even for use in children in Sub Saharan Africa, and more specifically Kenya as it does reduce incidences of transfusions in children with SCD.

The second aim of the study was to examine the dosage of HU and drug formulation used by these children with SCD. According to the National Heart Lung and Blood Institute, HU should be offered to all children, from infants 9 months of age at a recommended starting dose of 20mg/kg/day to a maximum of 35mg/kg/day [18]. Analysis in our study revealed that majority of the participants were actually under-dosed as per the above guidelines, with 51 (79.7%) receiving a daily dosage of < 20mg/kg/day. Majority of these patients had access to only the capsule formulation of HU 53 (82.8%) which provided challenges to daily dosing and most patients (57.8%) where on alternate day dosing. A clinical response to treatment may be suboptimal due to under-dosing however analysis of a possible association between a higher rate of frequency of transfusion and under dosing showed no statistical significance (p=0.847). A documented decrease in frequency of blood transfusion was still reported and it might be concluded that such doses are unnecessary for all patients. However, evaluation of alternative dosage regimens may be needed for patients in sSA's LMICs such as Kenya. Health care workers and those involved in the management of children with SCD should still prescribe the required dose of HU under the current international guidelines, with an aim of giving daily doses of HU.

Our third objective was to describe adherence to HU and factors affecting adherence in children with SCD aged 1-18 years. Most of the parents/caregivers ensured that the children took HU as prescribed with 50 (78.1%) reporting good compliance to the drug. This is a higher incidence compared to that reported by Patel et al in 2010 whereby the average refill prescription rate was 58.4% [14]. In our study those who did not take the medication as required sited factors such as cost, lack of availability, forgetting to refill the prescription or lack of a prescription during industrial strikes by healthcare professionals among other factors leading to poor compliance. However, more formal strategies are required to identify barriers to prescription refills among children with SCD

as these contribute to poor management of these children. HU should be taken consistently to achieve maximum benefit of the drug. Forgetting to buy drugs which contributed to the most cause of poor adherence can however be corrected through patient education and sensitization on the benefits of drug adherence.

We also examined perceived participant side-effects of HU. Majority of the participants (87.5%) had not experienced any side effects with the use of HU. However, for the few who had experienced side-effects, nausea and vomiting were the most commonly reported side effects (6.2%). This is comparable to the study done by Randi et al in 2005 where 16 (10.5%) of the patients reported unwanted side effects [13]. HU was well tolerated among most children in our study with only 1.6% experiencing either diarrhoea, abdominal pains, alopecia, changes in nail colour or coughing which provides an additional positive aspect in the management of SCD using HU. However, these findings do not apply to long-term adverse effects which would require longer duration of follow-up that was not feasible in our study. All of the children in our study were using folic acid and oral penicillin V. This is in keeping with the current international guidelines, Evidence-Based Management of Sickle Cell Disease Expert Panel Report, 2014 whereby at least all children under 5-years of age should be on folic acid and oral penicillin V [4]. The concurrent use of these two drugs minimizes the chances of getting complications of SCD.

Limitations of the study

The study was carried out in Kenyatta national Hospital and Gertrude's Children Hospital and only include children with SCD that visit these two institutions. Due lack of a valid comparison group in the quasi-experimental design issues with internal validity of the study like maturation and history effect may not have been addressed adequately.

It is also possible that generalizability of the study may be limited by the fact the children studied are not a random sample of all children with SCD in Kenya and this may result in some level of confounding.

The patient population used in this study was selected based on their use of hydroxyurea. Therefore, the study sample does not capture the barriers and thoughts of individuals who have poor adherence to HU or who might have declined the use of HU or who have been on the medication for less than 6 months. Recall bias of the participants, poor record keeping and incomplete documentation in the patients' files were also limitations of the study.

CONCLUSION

The study suggests that HU reduces the frequency of blood transfusions in children aged between 1 year and 18 years. Most children with SCD who are followed up in KNH and Gertrude's hospital are given HU doses below the recommended doses of 20mg – 35mg/kg/day. Most children with SCD on HU do tolerate the drug well and are on appropriate adjunctive medications. It appears that this study population has good adherence. Further research could define how interventions to these barriers influence the outcomes of adherence to hydroxyurea. Our data supports the use of hydroxyurea therapy for the prevention of frequent blood transfusions in children and it is strongly recommended that the use HU should be considered for all children with SCA in Kenya.

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