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Original Article

Hydroxyurea adherence and treatment outcomes in pediatric sickle cell disease: a prospective cohort study

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ABSTRACT

Hydroxyurea is the primary treatment for sickle cell anemia. However, its clinical efficacy depends heavily on long-term adherence. This study aimed to evaluate the levels of adherence to hydroxyurea treatment in pediatric sickle cell anemia patients. The study also sought to identify side effects that might necessitate dose reduction or temporary discontinuation of hydroxyurea treatment. A prospective cohort study was conducted over 12 months with 147 children with sickle cell anemia attending Armed Forces hospitals in the Southern Region. Demographic data were obtained from the hospital's information system, along with data on HU dose, treatment duration, laboratory values, and SCD-related complications. Adherence was assessed using the Morisky Modification Adherence Scale (MMAS-8). Statistical analyses were performed using SPSS software. The mean HU dose was 19.8 ± 3.3 mg/kg/day, and 61.2% of patients demonstrated high adherence (MMAS ≥ 8). HbF levels were significantly higher among adherent patients (15.2% vs. 10.7%, $p < 0.001$). Following initiation of HU therapy, annual transfusions and SCD-related complications decreased significantly ($p < 0.001$). ROC analysis indicated that HbF (AUC 0.75, 95% CI 0.62–0.87) is a stronger predictor of adherence than MCV (AUC 0.57, 95% CI 0.37–0.77). Adverse effects requiring HU dose adjustment occurred in 12.9% of patients, the most common being neutropenia and elevated transaminase levels. Higher HU adherence is associated with improved hematological parameters, particularly HbF, and reduced morbidity associated with SCD. MCV alone is a suboptimal indicator of adherence compared to HbF. Enhanced adherence monitoring and patient education are essential to improve the therapeutic benefits of HU in pediatric SCD.

Keywords: Sickle cell anemia, Hydroxyurea, Fetal hemoglobin, Pediatric hematology

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Introduction

Sickle cell disease (SCD) is one of the most prevalent diseases worldwide, especially among children, accounting for 90% [1] and 75% of global cases [2]. It is a hereditary hemoglobinopathy characterized by recurrent vascular obstruction resulting from the transformation of red blood cells from their normal disc-shaped form to a sickle-shaped one, impeding blood flow to all

parts of the body. It also causes chronic hemolytic anemia, end-organ damage, and a significant reduction in quality of life and life expectancy. It also contributes to stroke and acute chest syndrome (ACS) [3]. The disease burden remains high across age groups, with frequent emergency department visits, hospital admissions, and worsening complications that increase morbidity and healthcare costs. The World Health Organization (WHO) reported the health costs of this disease in 2006 [4], with annual healthcare costs for affected patients exceeding US$2.4 billion [5]. Studies have also shown a high mortality rate among children with this disease [6, 7]. To alleviate the suffering of patients, physicians and those concerned with the disease sought suitable treatments that could reduce symptoms at relatively lower costs. Hydroxyurea (HU) (also called hydroxycarbamide) has been used and approved by the US Food and Drug Administration (FDA) for adults and by the European Medicines Agency (EMA) for adults and children over two years old with sickle cell anaemia [8, 9]. Its effectiveness in patients with SCD has been demonstrated. It plays a role in increasing fetal hemoglobin (HbF) and reducing hemolysis and vascular occlusion. In addition, it positively affects cell adhesion, morphology, and rheology [10]. Furthermore, hydroxyurea reduces the formation of volatile organic compounds and decreases the transformation of red blood cells into the sickle shape [1]. Despite its clinical benefits and relatively low cost compared to newer medications, hydroxyurea is underused, and adherence is often suboptimal [11, 12]. Real-world analyses and systematic studies have linked increased hydroxyurea exposure and improved adherence to better hematological parameters, such as HbF and MCV (mean corpuscular volume) and a clinically significant reduction in emergency room visits and hospital stays. Conversely, non-adherence impairs the drug's ability to prevent complications and increases healthcare utilization. These associations have been observed in pediatric and adult populations and across diverse care settings [12, 13]. A pediatric study showed that a steady increase in hydroxyurea to a mean dose of 29.5 mg/kg/day resulted in improved hematological parameters and positive disease efficacy [14, 15]. However, these results cannot be generalized across different settings (high-income and low-income), and variations in dosage and administration all contribute to differing outcomes [13, 16]. Adherence to hydroxyurea is influenced by multiple factors, including patients' beliefs and fears about the side effects of medication use, as well as certain socioeconomic barriers and the way medications are prescribed by healthcare providers [17, 18]. Increasing HU adherence is also considered a potential way to improve patient health outcomes and reduce healthcare utilization [19, 20]. Monitoring hydroxyurea adherence is challenging; therefore, measurement methods have been used in clinical and research settings to assess pediatric adherence [21, 22]. These methods include MCV and HbF levels, which have been shown to increase with hydroxyurea treatment [23-25]. Furthermore, Creary *et al.* (2020) reported a cross-sectional analysis of adherence data from 34 children with SCD in a six-month, one-arm HU adherence study using Spearman's correlation coefficient. They compared participants' adherence to pharmacy records, MCV, and HbF with adherence to treatment monitored via video-guided chemotherapy (VDOT). Given the pivotal role of continuous hydroxyurea exposure in achieving disease-modifying effects, there is a pressing need for updated data that define adherence levels in affected patients and elucidate the relationship between adherence thresholds and measurable treatment outcomes. Therefore, this study aimed to monitor mean corpuscular volume (MCV) and fetal hemoglobin (HbF) values in patients receiving hydroxyurea therapy for sickle cell anemia to assess whether they could be used as an indicator of treatment adherence. Additionally, the study sought to identify side effects that would necessitate dose reduction or temporary discontinuation of hydroxyurea therapy, thus providing a clearer understanding of how adherence and tolerability affect treatment outcomes in sickle cell anemia.

Materials and Methods

Study design and duration

This study employed a prospective cohort design conducted over 12 months.

Study area and setting

The study was carried out in the Pediatric Hematology Department at the Armed Forces Hospitals, Southern Region (AFHSR), Kingdom of Saudi Arabia. All eligible children with a confirmed diagnosis of SCD who were receiving hydroxyurea (HU) therapy and followed up at the pediatric hematology clinic were included.

Study population and sampling

The study population comprised children aged 5–13 years with SCD. Participants were selected through convenience sampling among patients attending regular hematology follow-up during the study period.

Inclusion and exclusion criteria

The study included individuals with a confirmed diagnosis of sickle cell disease who had received hydroxyurea therapy for ≥6 months prior to enrollment, as well as those with at least one fetal haemoglobin (HbF) and one mean corpuscular volume (MCV) measurement while on HU therapy. The exclusion criteria are having a history of macrocytic anemia unrelated to HU therapy, as well as individuals who have a chronic kidney disease or other chronic comorbidities influencing hematologic indices.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for skewed data. In contrast, categorical variables were presented as counts and percentages. Correlations between the variables were assessed using

Spearman's rank correlation coefficients. Diagnostic accuracy of MCV and HbF for identifying low adherence (MMAS-8 < 6) was assessed using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC) and 95% confidence intervals (CIs). Optimal thresholds were selected to maximize sensitivity and specificity, and corresponding diagnostic performance indices (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and likelihood ratios) were reported. Pairwise comparison of AUCs was conducted using the DeLong test. Independent samples t-test and Mann–Whitney U test for continuous variables, depending on normality, and chi-square / Fisher's exact test for categorical variables. Logistic regression analysis was not performed because only 12 low-adherence cases were available, resulting in fewer than the recommended 10 events per variable and <5 events in several categorical predictor levels, conditions that would yield unstable estimates. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Analyses were conducted using R software version 4.2.2.

Ethical considerations

This study was reviewed and approved by the Research Ethics Committee of Armed Forces Hospitals, Southern Region, Kingdom of Saudi Arabia (Approval No. AFHSRMREC/2024/Pharmacy/742).

Results and Discussion

Baseline characteristics of pediatric patients included in the study

The study included 147 pediatric patients with sickle cell disease, with a mean age of 8.5 years (SD 3.2), and slightly more than half were males (54.4%). The median weight was 21 kg (IQR 17–28). Laboratory values, averaged across the 12-month study period from patient records, showed a mean corpuscular volume (MCV) of 86.4 fL (SD 10), hemoglobin level of 9 g/dL (SD 0.9), and fetal hemoglobin (HbF) percentage of 14.8% (SD 5.6). Regarding disease complications, vaso-occlusive crisis was the most frequent (94.6%), followed by acute chest syndrome (57.1%), splenic sequestration (34%), invasive pneumococcal disease (21.1%), splenectomy (20.4%), and stroke (6.8%). Less common complications included iron overload (6.1%) and aplastic crisis (2%) **(Table 1).**

Table 1. Demographic, Laboratory, and Clinical Characteristics of Pediatric Patients with SCD on Hydroxyurea Therapy (N = 147)

Variable	Value Mean ± SD N (%)
Demographics	
Age (years)	8.5 ± 3.2
Sex	--
Female	67 (45.6)
Male	80 (54.4)
Weight (Kg)	21 (17–28)
Average Lab values across 12 months	
Mean corpuscular volume (Fl)	86.4 ± 10
Hemoglobin (mg/dL)	9 ± 0.9
Fetal Hemoglobin (%)	14.8 ± 5.6
History of SCD Complications	
Vaso-occlusive crisis	139 (94.6)
Acute chest syndrome	84 (57.1)
Splenic sequestration	50 (34)
IPD history	31 (21.1)
Splenectomy	30 (20.4)
Stroke	10 (6.8)
Iron overload	9 (6.1)
Aplastic crisis	3 (2)

Continuous variables are presented as mean ± SD or median (IQR); categorical variables as n (%).

Hydroxyurea dose and adherence

The mean hydroxyurea (HU) dose, calculated as the average daily dose over the 12-month study period from patient records, was 19.8 mg/kg/day (SD 3.3), with a mean maximum tolerated dose of 20.8 mg/kg/day (SD 3.8). Dose reduction or temporary suspension due to adverse reactions occurred in 19 patients (12.9%). Adherence, assessed using the Morisky Medication Adherence Scale (MMAS-8), had a median score of 8 (IQR 7–9), with 61.2% of patients classified as having high adherence, 30.6% medium adherence, and 8.2% low adherence **(Table 2).**

Table 2. Hydroxyurea Dose, Adherence Levels, and Clinical Outcomes Among Pediatric Patients with SCD

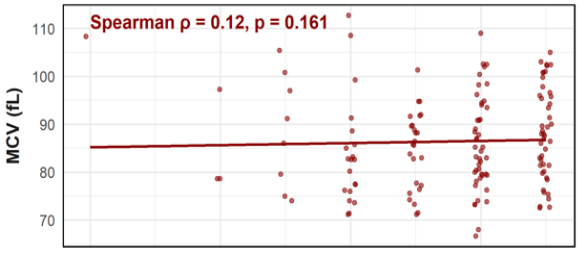
Variable	Total
Hydroxyurea dose	
Dose at beginning of study period (mg/kg/day)	17.5 ± 3.5
Dose at end of study period	21.5 ± 2.1

Average dose (mg/kg/day)	19.8 ± 3.3
Maximum tolerated dose (mg/kg/day)	20.8 ± 3.8
Hydroxyurea dose reduction or held due to Adverse reaction	19 (12.9)
Morisky Medication Adherence Score (MMAS) for Hydroxyurea use	
MMAS Score	8 (7–9)
Adherence level	
High (MMAS score ≥ 8)	90 (61.2)
Medium (MMAS score = 6 or 7)	45 (30.6)
Low (MMAS score < 6)	12 (8.2)
Outcomes before and after Hydroxyurea use	
Number of SCD-related transfusions per year	
Before Hydroxyurea	2 (1–3)
After Hydroxyurea	0 (0–1)
P	<0.001
Number of SCD-related complications per year	
Before Hydroxyurea	4 (3–6)
After Hydroxyurea	1 (1–2)
P	<0.001
ER visit or hospital Admission due to SCD complications	
Before Hydroxyurea	142 (96.6)
After Hydroxyurea	74 (50.3)
P	<0.001
Time elapsed from starting or increasing Hydroxyurea therapy until ER visit or hospital Admission due to SCD complications (Months)	
None	73 (49.7)
< 1 month	22 (15)
1 to < 6 month	27 (18.4)
6 months to < 1 year	15 (10.2)
Twelve months or more	10 (6.8)

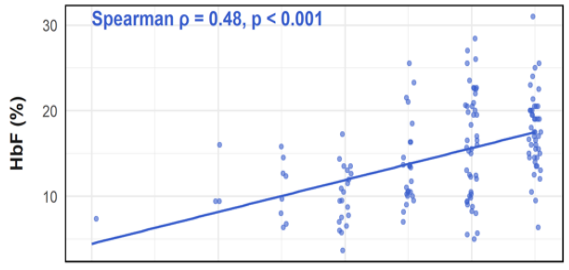
Average HU dose reflects the mean daily dose calculated across the 12-month study period as retrieved from medical records. Values are presented as mean ± SD, median (IQR), or frequency (percentage). P values were obtained using McNemar's test for binary outcomes and Wilcoxon signed-rank test for paired continuous variables. HU = Hydroxyurea; MMAS = Morisky Medication Adherence Scale; SCD = Sickle cell disease.

Correlation between HU adherence and laboratory markers

Hydroxyurea adherence, measured using MMAS-8, showed a weak and non-significant correlation with mean corpuscular volume (MCV) (Spearman's ρ = 0.12, p = 0.161). In contrast, fetal hemoglobin (HbF) levels demonstrated a moderate and statistically significant positive correlation with adherence (Spearman's ρ = 0.48, p < 0.001), indicating that higher HU adherence was associated with greater increases in HbF. Hemoglobin levels also showed a weak but statistically significant positive correlation with adherence (Spearman's ρ = 0.18, p = 0.026), suggesting that greater adherence to HU therapy was associated with slightly higher hemoglobin levels **(Figure 1)**.



a)



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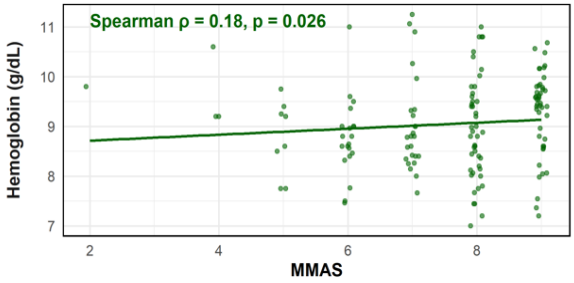

c)

Figure 1. Correlation of Hydroxyurea Adherence (MMAS-8) with MCV, HbF, and Hemoglobin Levels.

Diagnostic accuracy of MCV and HbF for predicting hydroxyurea adherence

Fetal hemoglobin (HbF) demonstrated good discrimination for detecting low adherence to hydroxyurea (HU), with an AUC of 0.75 (95% CI: 0.62–0.87, p < 0.001). At the optimal threshold of HbF ≤ 16%, sensitivity and negative predictive value (NPV) were both 100%, indicating that children with HbF > 16% can be reliably ruled out as having low adherence. However, HbF showed low specificity (42.2%) and a modest positive predictive value (PPV) of 75%, suggesting that many patients classified as

low adherers by this threshold may not truly have poor adherence. Likelihood ratios reflected this pattern, with LR− ≈ 0.00 (strong rule-out) and LR+ ≈ 1.73 (small rule-in effect). In contrast, mean corpuscular volume (MCV) did not demonstrate a statistically significant AUC, indicating limited diagnostic value in this context. Although HbF showed better performance than MCV (ΔAUC = 0.18, 95% CI: –0.10 to 0.45), the difference between the two markers was not statistically significant (p = 0.200) **(Table 3; Figure 2)**.

Table 3. Diagnostic Performance Indices of MCV and HbF for Identifying Low Hydroxyurea Adherence in Pediatric Patients with SCD

Indices	MCV	HbF
AUC (95% CI, p)	0.57 (0.37 to 0.77, p = 0.510)	0.75 (0.62 to 0.87, p < 0.001)
Best threshold	> 96.6	≤ 16
Sensitivity	41.7% (15.2 to 72.3%)	100.0% (73.5 to 100.0%)
Specificity	84.4% (77.2 to 90.1%)	42.2% (33.8 to 51.0%)
PPV	19.2% (6.6 to 39.4%)	75.0% (7.1 to 22.2%)
NPV	94.2% (88.4 to 97.6%)	100.0% (93.7 to 100.0%)
+ LR	2.68 (1.2 to 5.8)	1.73 (1.5 to 2.0)
- LR	0.69 (0.4 to 1.1)	0.0 (0.0 to 0.0)
Δ AUC $_{HbF - MCV}$	0.18 (-0.10 to 0.45), p = 0.200	

Outcome = low adherence (MMAS-8 < 6). Indices are shown as estimates with 95% confidence intervals.

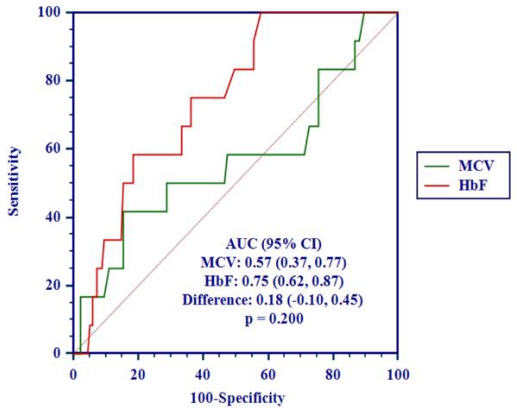

Figure 2. ROC Curves of MCV and HbF for Identifying Low Hydroxyurea Adherence in Pediatric Patients with SCD.

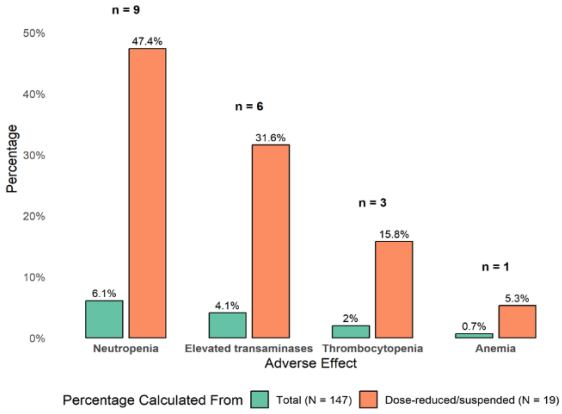

Figure 3. Distribution of adverse effects leading to hydroxyurea dose reduction or suspension among patients with SCD.

Adverse effects leading to hydroxyurea dose reduction or hold in patients with SCD

Neutropenia was the most frequent adverse effect leading to hydroxyurea dose reduction or suspension, occurring in 6.1% of the total cohort and representing 47.4% of patients who required dose modification (n = 9). Elevated transaminases were the second most common adverse effect, observed in 4.1% of the total cohort and accounting for 31.6% of those requiring dose adjustment (n = 6). Thrombocytopenia occurred in 2.0% of the overall population and represented 15.8% of patients with dose modification (n = 3). Anemia was rare, affecting only 0.7% of the cohort and 5.3% of patients who required dose reduction or treatment suspension (n = 1) **(Figure 3)**.

Comparison of patient characteristics by hydroxyurea adherence

No significant differences were observed between low-adherence patients (MMAS score < 6) and those with medium to high adherence (MMAS score ≥ 6) with respect to age, sex distribution, weight, or most average laboratory parameters. However, fetal hemoglobin levels were significantly higher among patients with medium-to-high adherence compared with those with low adherence (15.2% vs. 10.7%, p < 0.001). **In addition, the hydroxyurea dose at the end of the study period was significantly higher in the medium-to-high adherence group than in the low-adherence group (21.5 ± 2.1 vs. 18.5 ± 2.1 mg/kg/day, p < 0.001).** A history of vaso-occlusive crisis was less common in the low-adherence group than in the medium–high adherence group (75.0% vs. 96.3%, p = 0.019), whereas splenic sequestration was more frequent among low-adherence patients (75.0% vs. 30.4%, p = 0.003). Elevated transaminases leading to hydroxyurea dose modification occurred more often in the low-adherence group

(25.0% vs. 2.2%, p = 0.038). In addition, the median number of SCD-related complications per year before hydroxyurea therapy was higher in the low-adherence group (6.0 vs. 4.0, p = 0.002). Other variables—including mean corpuscular volume, hemoglobin level, hydroxyurea dosing indices, transfusions, and post-treatment outcomes—did not differ significantly between the two groups **(Table 4)**.

Table 4. Demographic, clinical, laboratory, treatment, and outcome characteristics of patients with sickle cell disease according to hydroxyurea adherence level

Variables	All Participants N = 147	Low Adherence (MMAS score < 6) N = 12	Medium to high Adherence (MMAS score ≥ 6) N = 135	P
Demographics				
Age (years)	8.5 ± 3.2	9.2 ± 3.4	8.4 ± 3.1	0.437
Sex				
Female	67 (45.6)	7 (58.3)	60 (44.4)	
Male	80 (54.4)	5 (41.7)	75 (55.6)	0.382
Weight (Kg)	21 (17–28)	22.5 (18.4–29.5)	21.0 (17.0–28.0)	0.409
Average Lab values across 12 months				
Mean corpuscular volume (Fl)	86.4 ± 10	89.3 ± 12.3	86.2 ± 9.8	0.403
Hemoglobin (mg/dL)	9 ± 0.9	9.1 ± 0.8	9.0 ± 0.9	0.882
Fetal Hemoglobin (%)	14.8 ± 5.6	10.7 ± 3.5	15.2 ± 5.7	**<0.001**
History of SCD Complications				
Vaso-occlusive crisis	139 (94.6)	9 (75)	130 (96.3)	0.019
Acute chest syndrome	84 (57.1)	10 (83.3)	74 (54.8)	0.070
Splenic sequestration	50 (34)	9 (75)	41 (30.4)	***0.003***
IPD history	31 (21.1)	0 (0)	31 (23)	0.071
Splenectomy	30 (20.4)	4 (33.3)	26 (19.3)	0.266
Stroke	10 (6.8)	0 (0)	10 (7.4)	1.000
Iron overload	9 (6.1)	2 (16.7)	7 (5.2)	0.159
Aplastic crisis	3 (2)	0 (0)	3 (2.2)	1.000
Hydroxyurea dose				
Dose at beginning of study period (mg/kg/day)	17.5 ± 3.5	18.5 ± 2.1	17.5 ± 3.5	0.333
Dose at end of study period	21.5 ± 2.1	18.5 ± 2.1	21.5 ± 2.1	***<0.001***
Average dose (mg/kg/day)	19.8 ± 3.3	19.9 ± 3.2	19.8 ± 3.3	0.929
Maximum tolerated dose (mg/kg/day)	20.8 ± 3.8	22.5 ± 4.9	20.7 ± 3.7	0.232
Hydroxyurea dose reduction or held due to Adverse reaction	19 (12.9)	3 (25)	16 (11.9)	0.189
Adverse effect that led to Hydroxyurea dose reduction or therapy suspension				
Anemia	1 (0.7)	0 (0)	1 (0.7)	
Elevated transaminases	6 (4.1)	3 (25)	3 (2.2)	***0.038***
Neutropenia	9 (6.1)	0 (0)	9 (6.7)	
Thrombocytopenia	3 (2.0)	0 (0)	3 (2.2)	
None	128 (87.1)	9 (75)	119 (88.1)	
Outcomes before and after Hydroxyurea use				
Number of SCD-related transfusions per year				
Before Hydroxyurea	2 (1–3)	3.0 (0.5–4.5)	2.0 (1.0–3.0)	0.206
After Hydroxyurea	0 (0–1)	0.0 (0.0–0.5)	0.0 (0.0–1.0)	0.792
Number of SCD-related complications per year				
Before Hydroxyurea	4 (3–6)	6.0 (6.0–8.5)	4.0 (3.0–6.0)	***0.002***
After Hydroxyurea	1 (1–2)	0.5 (0.0–2.0)	1.0 (1.0–2.0)	0.174
ER visit or hospital Admission due to SCD complications				
Before Hydroxyurea	142 (96.6)	12 (100)	130 (96.3)	1.000
After Hydroxyurea	74 (50.3)	7 (58.3)	67 (49.6)	0.765
Time elapsed from starting or increasing Hydroxyurea therapy until ER visit or hospital Admission due to SCD complications (Months)				
None	73 (49.7)	5 (41.7)	68 (50.4)	
< 1 month	22 (15)	4 (33.3)	18 (13.3)	
1 to < 6 month	27 (18.4)	3 (25)	24 (17.8)	0.297
6 months to < 1 year	15 (10.2)	0 (0)	15 (11.1)	
Twelve months or more	10 (6.8)	0 (0)	10 (7.4)	

Data are presented as mean ± SD, median (interquartile range), or n (%). p-values are based on an independent t-test, Mann–Whitney U test, or chi-square/Fisher's exact test, as appropriate.

The results showed that the mean hydroxyurea (HU) dose administered to the research group was 19.8 ± 3.3 mg/kg/day, with a mean maximum tolerated dose (MTD) of 20.8 ± 3.8 mg/kg/day. This aligns with common pediatric practice, where hydroxyurea is typically started at a dose of 15–20 mg/kg/day and then gradually increased to the individualized maximum tolerated dose. Quinn & Ware recommend increasing the MTD dose to maximize hematological response and clinical benefit [26, 27]. It was noted that 12.9% of the children had their dose reduced or were temporarily discontinued due to side effects experienced during treatment. However, the results also indicated that the majority of children who were treated with HU did not experience any side effects that would necessitate dose reduction or discontinuation. This indicates that the focus should not be on discontinuing the dose but rather on finding the correct dosage ratio that minimizes side effects [28-30]. Regarding the study sample's adherence to the prescribed dose, it was found to be relatively high, with 61.2% showing strong adherence and only 8.2% exhibiting low adherence. This highlights the role of healthcare in educating patients and encouraging them to use and adhere to their medication regimen. Conversely, a study by Madkhali and his colleagues on the same sample showed that over 81% of the sample did not adhere to the therapeutic dose (HU) due to side effects or a lack of patient health awareness [31, 32].

When comparing the results obtained after administering the therapeutic dose of HU, a significant improvement in clinical outcomes was observed, demonstrating a positive clinical effect and statistical significance. These large, clinically significant reductions reflect the findings of recent randomized trials and cohort studies showing that HU reduces transfusion needs, vascular occlusive events, acute coronary syndrome, and frequent hospital visits when patients receive and adhere to treatment [31, 33, 34]. The magnitude of the change we observed is consistent with the disease-modifying effects of HU in pediatric sickle cell disease. The time from the start of hormone replacement therapy to emergency department admission showed that 15.0% of patients were hospitalized within the first month, 18.4% within one to six months, 10.2% within six to twelve months, and 6.8% after twelve months or more. This time pattern is biologically plausible, as hematological responses to high-dose hydroxychloroquine (increased lipoglobulin and mean corpuscular volume) accumulate over weeks to months. Therefore, early events after treatment initiation may reflect prior disease severity or the time lag before the full therapeutic effect is achieved [28, 35]. These findings underscore the importance of clinical support during the first months of high-dose hydroxychloroquine therapy.

Although HU-induced macrocytosis may not directly indicate the correct HU dose [26, 36], MCV changes can be influenced by baseline hematological variation, nutritional status, and concomitant conditions [37, 38]. Therefore, we cannot always consider changes in MCV as an indicator of adherence, especially in children. In contrast, the moderately positive correlation (red) between MCV adherence and hemoglobin (HbF) levels highlights the biological and clinical significance of continuous HU exposure. Regular intake of HU increases hemoglobin production (HbF) by enhancing the gene expression of gamma globin, thereby reducing hemoglobin polymerization and the resulting vascular occlusion [39-41]. Recent pediatric and multicenter studies have shown that higher medication adherence or refill rates are positively associated with higher HbF levels and improved clinical outcomes, including reduced hospital visits [1, 42, 43]. These results confirm that hemoglobin levels (HbF) are a sensitive and dynamic indicator of HU adherence and effectiveness compared to MCV. This is consistent with previous studies suggesting the need for combined monitoring of laboratory biomarkers, including hemoglobin levels and MCV. [23, 44]. The positive correlation between MMAS and HbF observed in our cohort supports the inclusion of HbF monitoring in routine adherence assessments to guide early intervention for patients with poor treatment response.

The results of the diagnostic accuracy of MCV and HbF suggest that although HbF tends to perform better, the evidence is insufficient to confirm a statistically significant difference. In clinical hematology, HbF levels are frequently associated with disease severity and treatment response, particularly in hemoglobinopathies such as beta-thalassemia and sickle cell anemia (SCD) [45-47]. Elevated hemoglobin F levels have been shown to reduce hemolysis and improve oxygen transport, making hemoglobin F a more significant biomarker than red blood cell indices [48, 49]. These findings support the notion that hemoglobin F serves as a more robust biomarker than red blood cell size in characterizing disease states or predicting treatment outcomes, even if statistical significance is not achieved due to sample size or variability.

Considering the side effects leading to dose reduction or discontinuation of HU in sickle cell anemia patients, the most common toxicity was found to be neutropenia, followed by elevated transaminase levels and thrombocytopenia. The predominance of hematological toxicities, such as neutropenia and thrombocytopenia, is consistent with previous findings in therapies targeting erythropoiesis or hematopoietic modulation [50-52]. Neutropenia is particularly serious because it may lead to treatment delay or discontinuation, underscoring the importance of close hematological monitoring [53-55]. Overall, while the observed side effects are consistent with expected safety profiles, the relatively high dose adjustment rates suggest the need for individualized dosing strategies to improve tolerability, maintain efficacy, and avoid certain side effects.

Comparing patient characteristics based on their adherence to hydroxyurea (HU) highlights the crucial role of continued use in achieving therapeutic benefits in children with SCD. In this study, patients with moderate to high adherence (MMAS ≥ 6) exhibited significantly higher fetal hemoglobin (HbF) levels compared to those with low adherence, consistent with the relationship between HU use and the stimulation of HbF production [56, 57]. Elevated HbF levels are a key therapeutic indicator, as they reduce the incidence of sickle cell events, hemolysis, and vascular occlusions (VOEs) [58]. Interestingly, while a history of VOE was less common in the low-compliance group, this likely reflects selection bias or underreporting rather than a clinical benefit or fundamental correlation. Previous

studies have shown that poor HU adherence leads to higher VOE frequency and hospital admission rates [23, 59, 60] and also promotes patient comfort and reduces anxiety and stress [44, 61]. Conversely, splenic sequestration was more common among low-compliance patients, possibly due to insufficient HU exposure to protect the spleen, as early initiation of HU helps preserve both the spleen and kidneys [62]. Overall, these findings underscore that HU adherence is a key factor for treatment success, particularly for maintaining high HbF levels and reducing disease incidence. Interventions such as healthcare-associated patient education, digital reminders, and community programs have been shown to improve adherence and, consequently, significantly enhance outcomes [23, 63].

Conclusion

This study highlights that adherence to hydroxyurea (HU) therapy is a key determinant of positive clinical and hematological outcomes in pediatric sickle cell disease. It also plays a role in reducing vascular occlusions, the need for blood transfusions, acute chest syndrome, and other complications of SCD. Patients with higher adherence showed significantly higher fetal hemoglobin (HbF) levels and fewer disease-related complications and hospitalizations compared to those with low adherence. Furthermore, the study highlights the potential for further improving outcomes through dose optimization, objective monitoring of adherence, and targeted early follow-up at the start of treatment.

Recommendations

Routine monitoring of adherence using validated instruments shall be carried out in a timely manner to identify the candidates so that required interventions can be planned in a timely planned.

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Ethics statement: This study was reviewed and approved by the Research Ethics Committee of Armed Forces Hospitals, Southern Region, Kingdom of Saudi Arabia (Approval No. AFHSRMREC/2024/Pharmacy/742). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participating pediatric patients prior to enrollment.

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