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Differences in HRQOL among Children with SCD Who Received Hydroxyurea and Those Who Did Not: A Quantitative Comparison Study

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ABSTRACT

Objectives: Hydroxyurea is been recommended for patients with sickle cell disease (SCD) as it reduces the complications from the disease by increasing the production of fetal hemoglobin. In Oman, hydroxyurea is not consistently prescribed to children with SCD, and limited research has compared the health-related quality of life (HRQOL) among children prescribed hydroxyurea. Thus, this study evaluated HRQOL differences between children with SCD who received hydroxyurea and those who did not. ***Methods***: A cross-sectional study was conducted on children from a hematology clinic at a tertiary hospital in Oman. We collected the data using two questionnaires: HRQOL-SCD and HRQOL-Generic. A one-way analysis of variance was used for statistical analysis. ***Results:*** A total of 74 children (47.3% male and 52.7% female) completed the questionnaire; 33 children were on hydroxyurea and 41 were not. A significant difference in HRQOL scores was found between children receiving hydroxyurea and those not taking the drug [F (1,68) = 419.4; p-value = 0.001]. Regression analysis revealed that hydroxyurea was a significant predictor of improved HRQOL among children with SCD. An $R2$ of 0.87 indicated that 87.0% of the variability in the child-reported HRQOL-Generic was explained by parental familiarity, self-efficacy, child age, sex, and receiving hydroxyurea [$R2$ = 0.87, F (8,69) = 52.4; p-value < 0.001]. ***Conclusions:*** Hydroxyurea improved the children's HRQOL compared to those who did not receive the drug. These findings support the use of hydroxyurea in children to improve HRQOL and reduce vaso-occlusive episodes. We recommend increasing parents' understanding of hydroxyurea's significance and devising strategies to promote children's medication adherence. It is essential to modify the SCD management protocol to optimize the HRQOL among children with SCD.

Sickle cell disease (SCD) is a hereditary blood disorder classified as a hemoglobinopathy. This lifelong disorder is associated with many complications affecting multiple body systems.[1] In SCD, crescent-shaped red blood cells block the flow of blood to tissues, leaving them without enough oxygen.[2,3]

The main genetic types of SCD include hemoglobin SS, which is the most severe form, hemoglobin SC, and hemoglobin S beta thalassemia. Globally, the birth prevalence of SCD is estimated at 112 per 100 000 live births. Higher rates are reported in Africa, with 1125 per 100 000 live births, and in Europe with an estimated 43.12 per 100 000 live births. The number of individuals living with SCD globally increased from approximately 5.46 million in 2000 to about 7.74 million in 2021—a 41.4% increase. Meanwhile, the total number of neonates diagnosed annually rose by 13.7%, to approximately 515 000, driven mainly by population growth in the Caribbean and western and central sub-Saharan Africa.[4] These statistics illustrate the critical global burden of SCD on children, which highlights the need for targeted health interventions and evaluates the current management protocols.[5] In the United States of America, the SCD Association estimates that 70 000 to 100 000 individuals have SCD, and

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about 3 million carry the trait.[6] SCD predominantly affects African Americans according to the Centers for Disease Control and Prevention (CDC), with 1 in 500 African Americans affected, compared with 1 in 36 000 Hispanic Americans. Additionally, 1 in 13 African Americans carries the sickle cell trait.[6]

In Oman, SCD is a prevalent genetic blood disorder that increases the mortality and morbidity rates.[7] According to the Ministry of Health 2020 Annual Health Report, 309 school-age children are diagnosed with SCD each year and 286 preschool children were newly diagnosed, likely due to high rates of consanguinity marriages.[8] The birth prevalence of sickle cell trait in Oman is 6%, while beta-thalassemia is 2%, and SCD itself affects 0.2% of the population. Mortality is high, particularly in children under age five, with over 81 000 SCD-related deaths globally in 2021.[4,9] These statistics underscore the urgent need for improved screening, early intervention, and better access to effective treatments such as hydroxyurea.[4]

SCD causes various complications that negatively affect HRQOL in children. HRQOL is a significant patient-reported outcome in children and provides a detailed concept of SCD burden on children with SCD. Moreover,[10] it is a significant predictor of morbidity and mortality. One of these complications is a vaso-occlusive crisis, which is characterized by sharp and intense pain.[11] Vaso-occlusive pains occur around six times per year in children with SCD, and this pain may last up to four days.[12,13]

Painful episodes differ in prevalence and intensity.[14] Managing these painful episodes mainly starts in patients' homes, and sometimes, patients need hospital admission if the pain is persistent.[14] Vaso-occlusive painful episodes typically manifest as pain in the chest, back, or lower or upper limbs.[13] Extreme cold or hot environments, dehydration, the presence of other illnesses, and stress trigger these events.[15] Due to frequent vaso-occlusive pain events, children with SCD tend to have lower baseline HRQOL than healthy children.[15,16] SCD varies in severity (mild to severe); therefore, children with the more severe type of SCD usually present with worse HRQOL than those with the mild disease. Penicillin and blood transfusions are the usual treatments for children with SCD.[15] Recently, experts have recommended hydroxyurea drug therapy for patients with SCD. Hydroxyurea is a promising treatment option for SCD patients for reducing disease complications.[17] Although this medicine does not cure the disease, it does help make fetal hemoglobin (Hb F), which improves circulation and lowers the number of vaso-occlusive events.

Research has found that the use of hydroxyurea is associated with improvements in HRQOL.[15] Hydroxyurea has been studied and found to reduce chest syndrome episodes, painful crises, and the need for frequent blood transfusions or hospital stays.[10] Moreover, hydroxyurea could delay spleen infarction, kidney, lung, or even brain damage. It was found that the hydroxyurea drug could help the red blood cells remain stable and more flexible. Therefore, the red blood cells flow easily, even in tiny vessels. This occurs because hydroxyurea raises the level of Hb F, and thus, red blood cells do not change to a crescent shape. This results in fewer complications of the disease and better HRQOL of children with SCD.[7,10,15]

Research has suggested that children who were put on hydroxyurea became stable and quite asymptomatic, which decreased the burden of the disease among families and positively impacted the children's HRQOL. A cross-sectional study was conducted among children aged 3 to 18 years old to assess HRQOL in children with SCD.[18] Children in this study rated their HRQL less than their parents, but with no significant difference, except for social functioning ($p = 0.047$). Recruitment of children was conducted at hematology clinics, where they were requested to fill out the PedsQL survey. This study presented a significant difference ($p < 0.001$) in the total score of HRQOL of children who were taking the treatment daily (HRQOL score median = 75; IQR = 62.0–86.4) and those not (HRQOL score median = 69.0; IQR = 54.1–81.6). The study also proved that physical activities were significantly less when compared with those who did not start hydroxyurea (median = 71.4, IQR = 58.6; $p < 0.001$) than in children who were on hydroxyurea (median = 79.7; IQR = 62.5).[17] The non-users had several interferences with school attendance and lower scores in the physical domain compared to children who were adherent to the hydroxyurea drug.[17] Children who did not use hydroxyurea had frequent pain crises and complications that interfered with regular school attendance.[17]

Similarly, a qualitative study on medication adherence among children was conducted, involving

10 children and adolescents.[19] The study found that children experienced memory lapses, lacked self-management, and encountered barriers in their social life. This highlighted that HRQOL is affected among children with SCD. The researchers concluded that SCD children experience several barriers to medication adherence and urged the necessity for a comprehensive treatment plan to analyze the children's issues around medication adherence, which results in better HRQOL.

A cross-sectional study in Saudi Arabia concluded that children with low adherence to hydroxyurea perceived higher benefits in disease control (mean ± SD = 5.77 ± 2.99).[1] Another three studies investigated the impact of hydroxyurea adherence on the HRQOL among children with SCD.[11,16] The studies investigated the predictors of HRQOL in 78 with SCD (mean ± SD = 11.3 ± 3.92 years). Children completed the PedsQL during a clinic visit. The Adherence and Self-Care Inventory tool was utilized to measure treatment adherence. Results revealed that HRQOL is correlated with hydroxyurea adherence (R = 0.88). Adherence to hydroxyurea was a significant predictor of the improvement in the HRQOL scores.[11,16]

Not all children in Oman are prescribed hydroxyurea, and there is limited information about its use and HRQOL among children with SCD. Therefore, further assessment of HRQOL's impact is deemed important to examine its effects on HRQOL among children with SCD. In addition, no similar studies have been conducted in Oman, and to the best of our knowledge, this is the first study of this kind. Therefore, this study sought to investigate the differences in HRQOL between children on hydroxyurea treatment and those not on treatment. We hypothesized that children receiving hydroxyurea would report higher HRQOL scores and that hydroxyurea use would significantly predict improved HRQOL.

METHODS

This cross-sectional study included children aged 8–12 years from the Royal Hospital's hematology clinic in Oman. Participants were selected via simple random sampling based on even-numbered entries in clinic appointment lists. Sample size was determined using Slovin's formula with a 95% confidence level and 5% margin of error, accounting for a 10% attrition rate. A sample of 74 was deemed appropriate.

We used HRQOL-SCD (43 items, 9 domains, reliability = 0.93) and HRQOL-Generic (PedsQL, 23 items, 4 domains, reliability = 0.95). Both tools were validated in prior studies on children with SCD.[20,21,22]

SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) was used for data analysis. Scores were reverse-scored to a 0–100 scale; higher scores indicated better HRQOL. Normality, linearity, multicollinearity, and independence of errors were tested. One-way analysis of variance and analysis of covariance were conducted, and p-values < 0.05 were considered statistically significant. Linear regression identified predictors of HRQOL.

Ethical approval was obtained from the Ministry of Health (MOH/CSR/22/25828). Informed assent and consent were collected from children and their parents, respectively. Children were asked to fill in the two tools on HRQOL (child versions).

RESULTS

A total of 74 children (47.3% male, 52.7% female) completed the questionnaire; 33 were on hydroxyurea and 41 were not [Table 1]. A one-way analysis of variance was conducted to investigate the differences in HRQOL of children who receive hydroxyurea in comparison to those who do not.

The findings revealed a significant difference in HRQOL scores [Table 2] between children receiving hydroxyurea and those not (HRQOL-SCD) (F (1, 68) = 419.4; p < 0.001). Children on hydroxyurea reported higher HRQOL scores than children who were not (69.3 ± 10.1 and 51.5 ± 7.9, respectively).

Similarly, the findings showed no significant difference in HRQOL scores reported on the PedsQL-generic (F(1,68) = 239.8; p = 0.300). Children on hydroxyurea reported higher HRQOL scores than children who were not (68.5 ± 11.9 and 61.9 ± 14.9, respectively).

Furthermore, the study identified the predictors of HRQOL, and hydroxyurea appeared as a significant predictor for the improvement of HRQOL in children with SCD. Compliance with the hydroxyurea drug ($\beta = 2.40$, $t = 1.31$, $p = 0.010$, partial $\eta 2 = 0.16$) was a significant predictor of the child-reported HRQOL-Generic. The $R2$ of 0.87 showed that 87.0% of the

Table 1: Children's demographics, N = 74.

Variables	Mean (%)
Age, mean ± SD, years	10.0 ±1 .3
Sex	
Male	35 (43.7)
Female	39 (52.7)
On hydroxyurea	33 (44.6)
Not on hydroxyurea	41 (55.4)

variability in the child-reported HRQOL-Generic was explained by parental familiarity, self-efficacy, child sex, and receiving hydroxyurea ($R2$ = 0.87, F (8,69) = 52.4; p-value < 0.001) [Table 3].

Furthermore, the use of the hydroxyurea drug appeared to be a significant predictor in the HRQOL-SCD disease-specific tool (β = 5.18, t = 3.52; p = 0.001, partial η^2 = 0.41). The R^2 of 0.79 indicated that 79.0% of the variability in the child-reported HRQOL-SCD was accounted for by parental familiarity, self-efficacy, child gender, and use of hydroxyurea (R^2 = 0.79, F (8,69) = 29.59; p < 0.001) [Table 3]. In addition, the study examined a three-way interaction between sex, hydroxyurea, and HRQOL scores. The results showed that

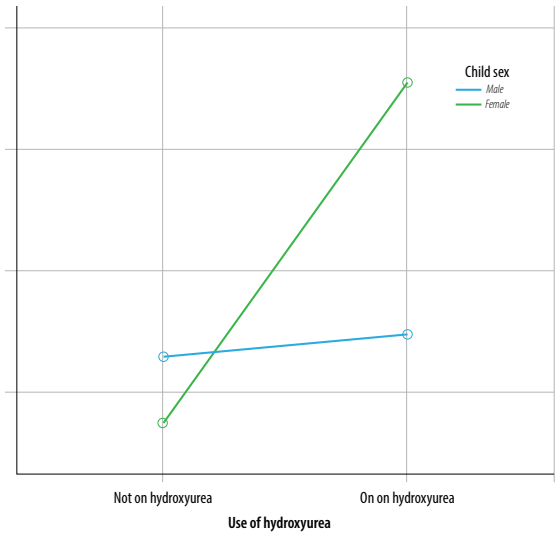

Figure 1: Three-way interactions between sex, hydroxyurea, and health related quality of life scores.

females on hydroxyurea reported higher HRQOL scores than male children (69.0 ± 11.1 and 64.7 ± 14.0, respectively); however, the difference was not significant. Figure 1 suggests a non-significant interaction between sex, hydroxyurea, and HRQOL (F (1,68) = 238.8; p = 0.500).

Table 2: Mean differences in health-related quality of life (HRQOL) scores (N = 33).

Use of hydroxyurea	Mean ± SD
HRQOL-SCD	
On hydroxyurea	69.3 ± 10.1
Not on hydroxyurea	51.5 ± 7.9
HRQOL-Generic	
On hydroxyurea	68.5 ± 11.9
Not on hydroxyurea	61.9 ± 14.9
Female (n = 17) on hydroxyurea	69.0 ± 11.1
Male (n = 16) on hydroxyurea	64.7 ± 14.0

Table 3: Predictors of health-related quality of life (HRQOL).

	Unstandardized coefficients		Standardized coefficients	t	Sig.	95% CI for β	
	β	Std. Error	β			Lower bound	Upper bound
Constant							
Use of hydroxyurea (HRQOL-SCD tool)	5.187	1.474	0.216	3.520	0.001	2.240	8.134
Use of hydroxyurea (PedsQL-generic tool)	2.407	1.837	0.063	1.310	0.010	-0.837	6.467

*RQOL-SCD **R square: 0.79, F-test = 29.59 and p < 0.001, PedsQL-Generic **R square: 0.87, F-test = 52.4 and p < 0.001.*

DISCUSSION

This study contributes valuable evidence on HRQOL in Omani children with SCD. Moreover, the uniqueness of the study is that females showed higher HRQOL. The findings align with global research: hydroxyurea improves HRQOL, reduces complications, and enhances overall well-being.[15,18]

The results of the study indicated that children with SCD who were receiving hydroxyurea reported higher HRQOL scores than children not using the drug. Our findings were similar to those of other studies, which found that hydroxyurea users had higher QOL scores than non-users.[11]

The non-users had several interferences with school attendance and lower scores in the physical domain. Also, similar findings were reported in previous studies, which concluded that participants with higher hydroxyurea adherence perceived more benefits and had better emotional outcomes.[16] The results from those studies revealed that adolescents with more negative perceptions of using hydroxyurea reported worse fatigue, pain, anxiety, and depression. Our findings showed that hydroxyurea was a significant predictor of the improvement in HRQOL. The finding is consistent with other studies, which identified hydroxyurea as a significant predictor for the improvement of QOL scores.[22] In addition, the study concluded that adherence to the drug was a significant predictor of improvement in the HRQOL scores.[22]

The finding has demonstrated that the use of hydroxyurea is associated with improvements in HRQOL. It was found that hydroxyurea treatment increases the amount of Hb F, and therefore, red blood cells are less likely to change into a sickle shape. This, in turn, leads to fewer complications of the disease and improves the HRQOL of children with SCD.[23,24] Furthermore, females on hydroxyurea reported slightly better outcomes, possibly due to higher adherence, although this warrants further exploration.

The study was a cross-sectional investigation and the data was collected only at one point in time. The small sample size limits the generalization of the findings. In addition, we did not measure medication adherence. We did not evaluate healthcare utilization for SCD patients, including number of visits and hospitalization, to correlate them with hydroxyurea use. Future studies should use randomized controlled trials with larger samples and examine additional variables such as hospitalizations and Hb F levels.

CONCLUSION

The use of hydroxyurea was associated with an improvement in HRQOL; children with SCD who were compliant with hydroxyurea reported higher HRQOL scores than children who were not using the drug. Hydroxyurea treatment results in fewer complications of the disease and better HRQOL in children with SCD. Therefore, we recommend enhancing parents' understanding of the significance of hydroxyurea and devising strategies to promote children's medication adherence. It is recommended to include in the SCD management protocol that all children with SCD take hydroxyurea drugs to reduce disease complications and improve their HRQOL.

Disclosure

The authors declare no conflicts of interest. No funding was received for this study. Written informed consent was obtained from one of the patient's parents, and an assent form was taken from the children who participated in the study.

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