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RESEARCH ARTICLE

# Hydroxyurea usage awareness among patients with sickle-cell disease in Saudi Arabia

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## Abstract

**Background and aim:** Hydroxyurea (HU) plays an essential role in the complex pathophysiology alteration of sickle-cell disease (SCD), which translates clinically into the enhanced quality of life and increased survival. This research examines adult patients with SCD's attitudes and awareness toward HU, as well as underutilization consequences.

**Method:** A cross-sectional research was performed in Saudi Arabia, and adult patients with SCD were interviewed. The survey includes patient demographics, attitudes, and knowledge of HU and clinical data. The chi-square was applied through SPSS version 23 for assessing any association with outcome variables and demographic characteristics.

**Results:** HU is known to 72 (67.3%) of the 107 patients. The hydroxyurea treatment was initiated in 46 patients (63%). Of these, 23 (50%) discontinue HU, with the key factors being pregnancy preparation and side effects development. For those who were unaware of HU, 13 (37.1%) were admitted to the intensive care unit because of acute chest syndrome, 29 (82.8%) required a frequent blood transfusion and 12 (34.2%) with frequent hospitalizations. However, there was no significant relationship between awareness and education level (*P* value is .078 > .05). In addition, there was no significant relationship between the level of awareness and age and gender of participants (*P* value is .68 and .44, respectively).

**Conclusion:** HU is a long-established and effective disease-modifying agent for SCD patients, but it is underutilized. The causality of underuse is bidirectional between patients and healthcare providers. It is essential to educate healthcare providers and patients with SCD about hydroxyurea role in modifying disease severity, resolving adverse events, and achieving full benefits.

KEYWORDS
adherence, hydroxyurea, sickle-cell disease

## 1 | INTRODUCTION AND BACKGROUND

Hemoglobinopathies are the most common inherited disease in humans. Sickle-cell disease (SCD) is one of the hemoglobinopathy disorders that has received significant attention from the global public health community due to its impact on increased mortality and morbidity.[1] Worldwide SCD incidence in newborns was estimated to be 300 000 in 2008.[1] Saudi Arabia is considered one of the countries with the highest prevalence of SCD. The prevalence rate of SCD is estimated to be 48.34 per 1000, according to data obtained from the premarital screening program between 2011 and 2015.[2]

A hallmark of SCD is intense pain leading to hospitalization and poor quality of life. This pain is experienced either as acute episodes or as chronic ongoing pain. Aborting the painful attack by targeting the pathophysiologic mechanism could potentially prevent or minimize tissue damage at the prodromal phase.[3,4] Similarly, introducing a novel agent such as hydroxyurea (HU) modifies the complex pathophysiology of SCD. This is translated clinically into reduced hospitalization, blood transfusion, improved quality of life, and the burden of SCD on institutions providing health care.[5]

Despite being approved as modifying agents for SCD for several decades, studies demonstrate the underutilization of HU among adult patients with SCD due to different beliefs and attitudes. Furthermore, a proportion of patients with SCD are almost entirely unaware of it.[5,6] Therefore, this work aims at evaluating adult patients with SCD attitudes and awareness toward HU in Saudi Arabia and their underutilization impacts.

## 2 | MATERIALS AND METHODS

This was a cross-sectional study conducted in Saudi Arabia's eastern province, where SCD is more common than that in other regions. A trained study team member interviewed a patient with SCD. It took approximately 10 to 15 minutes. The questions cover patient demographics such as age, gender, educational level, and clinical data such as comorbidities, frequency of hospitalization, blood transfusion, previous surgeries, intensive care unit hospitalization, and attitude and awareness of Hydroxyurea.

We considered hospitalization frequent if it occurred more than twice per year in the previous 2 years. On the other hand, we consider blood transfusion significant if it happens more than five times in a patient's life, despite the literature lacking a clear definition of significant blood transfusion in SCD patients.

Data were collected and analyzed using the International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 23. The descriptive analysis was performed to show mean, median, and mode values with SD (SD) for quantitative data. Begin

**TABLE 1** Demographic and general characteristics (n = 107)

| Continuous data | Descriptive analysis | | | |
|---|---|---|---|---|
| | Mean | Median | SD | 95% CI |
| Age in years | 29.53 | 28 | 11.14 | 27.21-31.48 |
| Number of hospitalization/y | 4.54 | 2.00 | 4.44 | 3.69-5.39 |
| Number of emergency visits/y | 8.08 | 7.00 | 5.48 | 7.03-9.14 |
| Frequency of ICU admission/y | 2.41 | 1.00 | 2.91 | 1.85-2.97 |
| Number of transfusion/y | 5.89 | 5.00 | 4.24 | 5.07-6.70 |
| **Categorical data** | | | | **Frequency (%)** |
| Level of education | | Higher | | 25 (23.3%) |
| | | Intermediate School | | 08 (7.3%) |
| | | Secondary school | | 61 (64.3%) |
| | | Primary school | | 13 (12.1%) |
| Gender | | Male | | 32 (29.9%) |
| | | Female | | 75 (70.1%) |
| Blood transfusion was done | | Yes | | 92 (85.9%) |
| | | No | | 15 (14.1%) |
| Use hydroxyurea | | Yes | | 46 (42.9%) |
| | | No | | 61 (57.1%) |
| Intensive care unit Admission | | Yes | | 49 (45.7%) |
| | | No | | 58 (54.3%) |
| Any comorbidity | | Stroke | | 02 (1.8%) |
| | | Splenectomy | | 16 (14.9%) |
| Awareness about hydroxyurea medication in sickle-cell patients | | Yes | | 72 (67.3%) |
| | | No | | 35 (32.7%) |

**TABLE 2** Impact of hydroxyurea on the clinical of the patient with sickle-cell disease

| | On hydroxyurea | Unaware of hydroxyurea | *P* value |
|---|---|---|---|
| ICU admission | 9 (19.5%) | 13 (37.1%) | .99 |
| Frequent blood transfusion | 18 (39.1%) | 29 (82.8%) | .01 |
| Frequent hospitalization | 15 (32.6%) | 12 (34.2%) | .01 |

**TABLE 3** Comparison of reasons for not using hydroxyurea medication and demographic variables (n = 107)

| Variables | Reasons | Subjects | | | | *P* value |
|---|---|---|---|---|---|---|
| Age groups | | 14-24 y | 25-35 y | 36-45 y | 45 and above | .99 |
| | Fear | 8 | 6 | 2 | 2 | |
| | On hydroxyurea | 17 | 16 | 8 | 3 | |
| | Preference | 17 | 19 | 3 | 6 | |
| Educational level | | Graduates | Secondary | Primary | Illiterate | .01 |
| | Fear | 4 | 12 | 2 | 0 | |
| | On hydroxyurea | 9 | 26 | 8 | 1 | |
| | Preference | 12 | 23 | 3 | 7 | |
| Gender | | Female | | Male | | .01 |
| | Fear | 14 | | 4 | | |
| | On hydroxyurea | 28 | | 16 | | |
| | Preference | 33 | | 12 | | |

the analysis by determining the data's normality. The normally distributed data were analyzed, and mean values with SD were calculated (SD). The one-sided hypothesis was tested for the categorical data analyzed, and chi-square was applied to assess any association among different variables. A *P* value less than .05 was considered a significant level.

The approval was obtained from King Faisal University's Ethical Committee. The purpose of the study, the use of data, the benefits of doing this research, confidentiality, and data anonymity were all explained to participants.

## 3 | RESULTS

Attitude and awareness of hydroxyurea were evaluated among 107 patients with SCD. The participants' ages range from 14 to 60 years, with a median age of 29.35 ± 11.1. Demographic and general characteristics are shown in Table 1.

Out of 107 patients, 72 (67.3%) are aware of hydroxyurea. Forty-six patients (63%) started on hydroxyurea. Of these, 23 (50%) discontinue hydroxyurea, with the main reasons for discontinuation are planning for conception, pregnancy, and the development of side effects, particularly cytopenia and hair loss. On the other hand, 26 (36%) were not on hydroxyurea either due to personal preference or fear of adverse effects.

For those who were unaware of hydroxyurea, 13 (37.1%) were admitted to the intensive care unit because of acute chest syndrome, 29 (82.8%) required a frequent blood transfusion, and 12 (34.2%) with frequent hospitalizations. Of note, there was a significant relationship between being on hydroxyurea and the frequency of blood transfusion and hospitalizations (*P* value is .01 < .05). Conversely, the relationship was not significant with the admission to the ICU. Table 2.

There was a significant relationship between awareness and education level (*P* value is .01 > .05). In addition, there was a significant relationship between the level of awareness and gender of participants but not with age (*P* value is .01 and .99, respectively). Table 3.

## 4 | DISCUSSION

In SCD, red blood cell deoxygenation results in intracellular polymerization of the abnormal HbS molecule and rapid, reversible shape change. Erythrocyte sickling leads to a broad range of acute and chronic clinical complications caused by repeated ischemia, inflammation, predominantly painful crisis, and acute chest syndrome. Erythrocyte re-oxygenation breaks down the HbS polymer and restores the normal shape.[7]

Several treatment options established and proved their role in treating patients with SCD. These include hydroxyurea, L-glutamine, crizanlizumab, and voxelotor.[7,8] Hydroxyurea is the oldest one among the previously mentioned options though it is a safe and effective treatment and provides therapeutic benefits through several action mechanisms. These mechanisms include increasing hemoglobin F levels and reducing hemolysis through improved erythrocyte hydration and reduced intracellular sickling. In addition, it lowers neutrophil and reticulocyte counts from ribonucleotide reductase inhibition and

marrow cytotoxicity, resulting in decreased adhesiveness and vaso-occlusion. Furthermore, hydroxyurea increases the local release of nitric oxide with potential local vasodilatation and improved vascular response.[9,10]

After more than 25 years of follow-up, hydroxyurea is proven to be associated with improved survival without accompanying serious adverse events.[11] Nevertheless, attitudes of the patient with SCD toward hydroxyurea are variable. The previous study reveals that patient perception was reflected significantly on adherence to the treatment. On the other hand, misinformation about hydroxyurea and lack of insight translated into initiation refusal or therapy discontinuation.[12,13]

Our study showed that despite hydroxyurea being in the market for several decades, around one-third of participants are unaware of it rather than having a barrier to take it, as previously reported.[12] In addition, there were poor correlations between awareness and age, gender, and education level. Furthermore, most of those unaware of hydroxyurea do have an absolute indication for treatment initiation though not offered. On the contrary, many aware individuals prefer not to be initiated on or discontinue hydroxyurea usage due to either fear of or experiencing side effects, respectively. These findings are consistent with the result from a previous study indicating that having insight about medications and routine outpatient monitoring has a significant role in adherence and acceptance of treatment.[14] In addition, this study enlightens the clinical community about a bidirectional causality for hydroxyurea underuse between patients and healthcare providers.

Hydroxyurea-treated individuals with SCD demonstrated a significant reduction in vaso-occlusive events, acute chest syndrome, hospitalizations, and blood transfusions.[15] Conversely, our study did not reveal a significant reduction in acute chest syndrome. We assume that these findings might be explained by poor compliance or lack of awareness of the maximum tolerated dose (MTD) concept.[9]

The literature does not show many publications addressing the awareness level of hydroxyurea among adult patients with SCD and its impact on their attitude and adherence. In addition, this study shows that a good percentage of healthcare providers did not offer hydroxyurea despite being indicated, which might be due to either lack of knowledge or experience. However, some limitations might influence the results of this study. First, the sample size might be small enough to represent the whole population with SCD. Second, our research data lack hydroxyurea when people stop it either because of experiencing side effects or lack of response. This is a crucial point reflecting awareness of the MTD concept among physicians.

## 5 | CONCLUSION

Many treatment paradigms for SCD patients have emerged. Hydroxyurea is still an efficient and safe medication of choice, although it is under-prescribed by healthcare providers and unappealing to many patients. This study's findings warrant further investigation to accurately reflect physician attitude toward hydroxyurea prescription and their responses when side effects exist. Furthermore, it also highlights the importance of assessment by field specialists to explore all resources and available treatment options. Finally, mass education to healthcare providers and SCD patients about the importance of hydroxyurea in modifying disease severity, overcoming adverse events, and reaching maximum benefits are needed.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest to be disclosed.

## AUTHOR CONTRIBUTIONS

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All authors have read and approved the final version of the manuscript.

Mortadah Alsalman had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

## TRANSPARENCY STATEMENT

Mortadah Alsalman affirms that this manuscript is an honest, accurate, and transparent account of the reported study; no essential aspects have been omitted. Any discrepancies from the study as planned have been explained.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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