*https://doi.org/10.31925/farmacia.2024.4.24* **ORIGINAL ARTICLE**

# EFFECT OF HYDROXYUREA ON PULMONARY FUNCTION TESTS AND HAEMATOLOGICAL PARAMETERS IN ADULT PATIENTS WITH SICKLE CELL ANAEMIA

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**Abstract**

It was established that hydroxyurea has numerous advantages for patients with sickle cell anaemia (SCA), including a decrease in different complications of this serious disease, such as acute chest syndrome. This study was conducted to reveal the effect of hydroxyurea on pulmonary function tests, as a primary point, and on haematological values, as a secondary point, in patients with SCA. This was a cross-sectional study carried out in Iraq, in which 208 participants were recruited and categorised into three groups: Group 1 included 74 healthy adults; group 2 included 64 SCA patients who didn't take hydroxyurea; and group 3 included 70 SCA patients on hydroxyurea. Measurement of pulmonary function tests and haematological values was performed for all groups. Pulmonary function tests revealed significant variations between group 1 and each of groups 2 and 3, while they showed no significant variation between groups 2 and 3. On the other hand, haematological values revealed significant variations ($p<0.05$) when comparing the two groups. Hydroxyurea has contributed to improving the haematological profile of CSA patients, but it has not been proven to have any positive effect on the pulmonary function tests, despite what was previously published to be effective in reducing the respiratory complications caused by sickle cell anaemia.

**Rezumat**

În cadrul acestui studiu a fost evaluat efectul hidroxiureei asupra funcției pulmonare și asupra valorilor hematologice, la pacienții cu anemie falciformă. S-a efectuat un studiu transversal, în care au fost incluși 208 participanți din Irak, împărțiți în trei grupuri astfel: primul grup a cuprins 74 de adulți sănătoși, al doilea 64 de pacienți cu anemie falciformă care nu au primit hidroxiuree, iar al treilea grup 70 de pacienți cu anemie falciformă care au primit hidroxiuree. Măsurarea testelor funcției pulmonare și a valorilor hematologice a fost efectuată pentru toate grupurile. Testele funcției pulmonare au evidențiat variații semnificative între grupul 1 și fiecare dintre grupurile 2 și 3, în timp ce între grupurile 2 și 3 variațiile nu au fost semnificative. Hidroxiureea a contribuit la îmbunătățirea profilului hematologic al pacienților cu anemie falciformă, dar nu a dovedit efecte pozitive asupra testelor funcției pulmonare.

**Keywords**: pulmonary function tests, haematological values, sickle cell anaemia, hydroxyurea

## Introduction

Sickle-cell anaemia (SCA) is a monogenic, haematological and multi-system disease distinguished by recurrent episodes of acute disease exacerbations that cause organ destruction. It has been reported that the number of people with SCA will more than double from 305,800 in 2010 to 404,200 by 2050 [1]. End-organ destruction is linked to the majority of SCA-related deaths [2, 3], and pulmonary complications are a common cause of morbidity and mortality. It was approved that adults with SCA have progressive pulmonary function tests (PFT) alterations, including a decrease in lung volumes and flows, as a result of airflow limitation and airway hyperresponsiveness, which are associated with increased morbidity and premature death [4, 5]. Acute chest syndrome (ACS), pulmonary hypertension (PH), lower airway obstruction and airway hyperresponsiveness (AHR) are pulmonary consequences of SCA. Growing evidence points to recurrent episodes of ACS as a significant risk factor for sickle-cell-associated chronic pulmonary illness. ACS shows a pathological chain of events, including pulmonary infarction, inflammation and atelectasis, that leads to a mismatch between ventilation and perfusion and a rise in pulmonary artery pressure. Moreover, the changes in the parenchyma and vessels of the lung that take place during the haemolysis may contribute to the development of PH in SCA [6, 7].
In 1995, the Multicenter Study of Hydroxyurea in Sickle Cell Anaemia provided the first evidence of hydroxyurea's effectiveness in treating adults. According to the MSH, there has been a significant decline in the median yearly rate of unpleasant events, acute chest syndrome episodes and transfusions. The clinical impact of HU is proposed to be mediated by its capability to

enhance foetal haemoglobin (HbF) expression in RBCs. The reduced level of foetal haemoglobin (HbF) is one of the best indicators of morbidity and mortality in A [8, 9]. HU also has a beneficial effect on RBC hydration and deformability that slow down haemolysis, and its capacity to reduce the number of circulating WBCs probably contributes to a reduction in endothelial inflammation and vasoocclusion. RBCs and endothelial cells exhibit fewer adhesion receptors when exposed to HU [10, 11]. Furthermore, HU releases a nitric oxide moiety that is characterised by its ability to reduce endothelial damage due to its vasodilatory actions in addition to reducing platelet and coagulation activity [12, 13]. HU lessens the vasoocclusive consequences associated with SCA in both children and adults. In people with SCA, long-term HU use has been shown to play a role in decreasing mortality and enhancing health-related quality of life [14]. Regardless of the clinical severity of SCA, children and adults should be treated with hydroxyurea (HU), which is now highly recommended to treat people with the SS and S/b0 genotypes of SCA [15]. It is considered a key component of medical therapy for SCA. It can prevent and treat both acute and long-term problems in SCA [16]. Recent research has switched to investigating the additional positive roles of HU in the complications of SCA [17, 18]. Two prior clinical trials have offered evidence about the ability of HU to reduce mortality in SCA and that long-term exposure could decrease the risk of SCA-related respiratory signs and complications that lead to death [19, 20], owing to the fact that HU treatment might lower the degree of hyperreactivity in respiratory passages in adults with SCA [21]. However, it is still unknown how it may affect the longitudinal decline in lung function tests. The purpose of the study is to investigate the role of HU medication in reducing PFT impairment in adult patients with SCA.

## Materials and Methods

This study is a cross sectional design, carried out at Thalassemia Centre of Clinical Genetics disorders in Basra City, Iraq. The work was done between November 2022 and the end of March 2023. It was carried out in accordance with the recommendations made by the STROBE statement (Strengthening the Reporting of Observational studies in Epidemiology) [22]. The protocol and informed consent were approved by the local ethical committee.

*Patients*

The study included 208 adult individuals at age range (18 - 42) years, categorized into three groups: Group 1 is 74 healthy individuals with mean of age (30.87 ± 10.77) who were from the college staff professional, academic and students. Group 2 is 64 sickle cell anaemia patients in steady states with mean of age (27.3 ± 9.21) they didn't take hydroxyurea therapy, were previously diagnosed with SCA based on electrophoresis and used to attend out-patient unit at Thalassemia Center of Clinical Genetics disorders.

The third group is Group 3, included 70 SCA patients who were on hydroxyurea therapy with mean age (29.51 ± 9.97). The patients were on hydroxyurea tablets in a weight dependent dose 15mg/kg/day as single dose with monitoring the patients' blood cell count every three months. The dose is not raised if blood counts are within acceptable range and with no toxic effect [23]. All the patients in group 3 were on the specific dose for at least three years.

A detailed form of questionnaire was used to gather and record information about each person's age, height, weight, body mass index (BMI), co-morbidities, anamnesis and lifestyle (drug use and smoking status). History of HU toxicity or hypersensitivity beside respiratory diseases, cardiovascular diseases, endocrine diseases, neuromuscular function disorders, physical abnormalities; smoking and pregnancy were all taken into consideration as exclusion criteria. The required data of spirometry results and complete blood count were measured for all groups of the study. The collected data transferred to an excel sheet and analysed statistically. The work was conducted in conformity with the World Medical Association's (WMA) Helsinki Declaration and patients' health was a priority.

*Spirometry*

In accordance with the American Thoracic Society (ATS) guideline [24], spirometry was performed and evaluated for all patients using a medical spirometer (MIR Spiro lab III Diagnostic Spirometer, Ltd. UK). The patients were asked to stand while performing spirometry, inhale fully, and then exhale as quickly and forcefully as they could through the MIR spirolab's mouthpiece. To record the best reading and the correct diagnosis as indicated by the equipment, the procedure was performed three times because it depends on each individual's cooperation. Forced vital capacity (FVC) in litres, forced expiratory volume in one second (FEV1), FEV1/FVC ratio, maximal voluntary ventilation (MVV), peak expiratory flow (PEF) and estimated lung age (ELA) were measured by the spirometer. To show the differences in lung parameters among the groups, absolute values of pulmonary function tests were measured. Spirometry data may be interpreted as a normal, obstructive, restrictive, or mixed case depending on the criteria of ATS [25]. The American Thoracic Society (ATS) standards describe normal lung function as having normal FVC and FEV1 values. A restrictive pattern is defined when FVC is below 80%. An obstructive pattern is found when FEV1 is below normal; FVC is normal and the FEV1/FVC ratio is below 70%. The combined pattern (restrictive and obstructive disease) is identified when both FVC and the FEV1/FVC ratio are declined [26].

*Haematological measurements*

Complete blood measurements were done by collecting nearly 5 mL of venous blood in ethylenediamine-

tetraacetic acid (EDTA). Red blood cell count (RBC), haemoglobin concentration (Hb) (g/dL), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), total count and differential count (neutrophils, monocytes and lymphocytes) were determined using flow-cytometry using (SYSMEX XT-2000i, Japan). Hb variations were detected using haemoglobin electrophoresis test.

*Statistical Analysis*

The data were analysed using the statistical package for social sciences (SPSS) (version 24.0). Means and standard deviations (SD) were used to represent continuous data, whereas percentages were used to represent categorical variables. While categorical variables were analysed using the nonparametric test (2 independent parameters), continuous variables were compared using the Mann-Whitney U and Wilcoxon W tests. p value less than 0.05 was regarded as a significant difference.

## Results and Discussion

A total of 208 individuals contributed to this study; three groups were categorised based on health status and HU therapy intake. The three groups had a non-significant difference in the mean age ($p < 0.05$), as well as no significant differences in gender distribution (males: females ratio), the percentage of males and females among the groups ($p < 0.05$), and an increase in male percentage in all of the groups, as illustrated in Table I. On the other hand, there were significant variations ($p > 0.05$) in weight, height and BMI between group 1 and each of groups 2 and 3. While no significant differences were found between groups 2 and 3 in these parameters.

As revealed in Table II, pulmonary function parameters show significant variations among the different groups of the study. The variations are represented by significant declines ($p > 0.05$) in each of FEV1, FVC, FEV1%, PEF and MVV in groups 2 and 3 when compared to group 1. While ELA is significantly elevated in groups 2 and 3, On the other hand, there are no significant changes between 2 and 3 in all pulmonary function tests ($p < 0.05$).

Regarding the haematological profile, significant variations among the three groups were found. There are significant variations ($p > 0.05$) between groups 1 and 2 in haematological parameters, as indicated by Table III, as well as significant variations ($p > 0.05$) between group 1 and group 3 (the group on HU therapy). Several parameters, such as WBC, lymphocytes, monocytes and neutrophils, were significantly decreased in group 3 when compared to group 2 ($p > 0.05$). While other parameters such as RBC, HGB and MCV were significantly increased in group 3 compared to group 2, as seen in Table III.

**Table I**

General characteristics of the groups

| Parameter | Group 1 Mean ± SD (n = 74) | Group 2 Mean ± SD (n = 64 | Group 3 Mean ± SD (n = 70 | p value 1 *vs.* 2 | p value 1 *vs.* 3 | p value 2 *vs.* 3 |
|---|---|---|---|---|---|---|
| **Age** | 30.87 ± 10.77 | 27.3 ± 9.21 | 29.51 ± 9.97 | 0.93 | 0.39 | 0.30 |
| **Gender (male:female)** | 38:36 | 34:30 | 37:33 | | | |
| **Male%** | 51.35% | 53.12% | 52.85% | 0.067 | | |
| **Female%** | 48.64% | 46.87% | 47.14% | 0.23 | | |
| **Weight** | 71.94 ± 18.32 | 56.77 ± 9.87 | 57.87 ± 11.10 | 0.000 | 0.000 | 0.57 |
| **Height** | 166.81 ± 13.49 | 160.65 ± 11.53 | 163.16 ± 8.86 | 0.002 | 0.004 | 0.38 |
| **BMI** | 28.29 ± 29.15 | 21.97 ± 2.93 | 21.64 ± 3.24 | 0.000 | 0.000 | 0.43 |

Data are significant when p value is < 0.05

**Table II**

Pulmonary function tests comparison in the three groups of the study

| Parameter | Group 1 Mean ± SD | Group 2 Mean ± SD | Group 3 Mean ± SD | p value 1 *vs.* 2 | p value 1 *vs.* 3 | p value 2 *vs.* 3 |
|---|---|---|---|---|---|---|
| **FEV1** | 3.19 ± 0.75 | 2.39 ± 0.81 | 2. 63 ± 0.87 | 0.000 | 0.000 | 0.63 |
| **FVC** | 3.22 ± 0.755 | 2.51 ± 0.77 | 2.76 ± 0.75 | 0.000 | 0.000 | 0.596 |
| **FEV1 %** | 101.28 ± 8.50 | 86.61 ± 9.78 | 89.05 ± 10.59 | 0.034 | 0.048 | 0.394 |
| **PEF** | 5.89 ± 2.06 | 3.19 ± 1.67 | 3.84 ± 1.23 | 0.000 | 0.000 | 0.375 |
| **ELA** | 47.23 ± 19.09 | 64.97 ± 19.94 | 61.03 ± 18.98 | 0.000 | 0.000 | 0.052 |
| **MVV** | 109.54 ± 22.88 | 75.83 ± 21.64 | 77.32 ± 20.35 | 0.000 | 0.000 | 0.765 |

Data are significant when p value is < 0.05

**Table III**

Haematological profile comparison among group 1, 2 and 3

| Parameter | Group 1 Mean ± SD | Group 2 Mean ± SD | Group 3 Mean ± SD | p value 1 *vs.* 2 | p value 1 *vs.* 3 | p value 2 *vs.* 3 |
|---|---|---|---|---|---|---|
| **WBC** | 6.71 ± 1.50 | 10.93 ± 4.77 | 9.01 ± 4.06 | 0.000 | 0.000 | 0.04 |
| **Lymphocytes** | 2.34 ± 0.75 | 3.78 ± 2.50 | 3.02 ± 1.78 | 0.002 | 0.02 | 0.031 |
| **Monocytes** | 0.60 ± 0.25 | 0.85 ± 0.57 | 0.76 ± 0.44 | 0.023 | 0.051 | 0.665 |
| **Neutrophils** | 4.47 ± 1.37 | 6.03 ± 3.22 | 4.69 ± 2.67 | 0.018 | 0.61 | 0.012 |
| **RBC** | 4.89 ± 0.627 | 3.27 ± 1.02 | 3.87 ± 0.80 | 0.000 | 0.023 | 0.048 |

| Parameter | Group 1 Mean ± SD | Group 2 Mean ± SD | Group 3 Mean ± SD | p value 1 *vs.* 2 | p value 1 *vs.* 3 | p value 2 *vs.* 3 |
|---|---|---|---|---|---|---|
| **HGB** | 13.61 ± 1.58 | 10.03 ± 2.37 | 11.42 ± 1.97 | 0.000 | 0.000 | 0.063 |
| **MCV** | 89.76 ± 6.58 | 86.94 ± 10.68 | 91.79 ± 15.35 | 0.002 | 0.039 | 0.006 |
| **MCH** | 30.13 ± 3.10 | 29.49 ± 3.97 | 30.89 ± 4.83 | 0.194 | 0.360 | 0.064 |

Data are significant when p value is < 0.05

The current study confirms a presence of significant declines ($p < 0.05$) in respiratory tests including FEV1, FVC, FEV1 %, PEF and MVV of group2, when comparing with a matched age healthy group (group 1). This finding could support the results of previous studies that showed abnormal PFTs in patients with SCA that represented by a restrictive pattern disorders [6, 27]**.** Moreover, a prior study has found a positive association between FEV% and Hb in sickle cell disease patients, which might be explained by the fact that the pathological process of sickle cell disease could result in respiratory disorders represented by reduced lung compliance and a decline in PFTs. As well as the reduced lung compliance has been linked to the development of pulmonary hypertension, chronic pulmonary disorders and recurrent episodes of acute chest syndrome that caused by sickle cell vasculopathy [28]. Another factor that represents an impairment in PFTs of SCA patients in the current work, is the significant increase in ELA in group 2 and 3 when comparing with group 1 ($p < 0.05$). ELA is the same real age when the person is healthy, without any respiratory symptom and his PFTs are normal, while an increase in ELA refers to a presence of respiratory disorder [26, 29]. There are no significant changes between 2 and 3 in all pulmonary function tests ($p > 0.05$), which indicated to that HU therapy didn't create a positive effect in ELA in the patients on the medication. In fact, no evidences were available in this field. The present work showed the negative impact of SCA on pulmonary function tests, even in patients on HU therapy. This may explain why we found significant decrease in all measured PFTs in patients who were on HU therapy. Group 3 showed significant decline in PFT when compared to healthy (group 1), as well they showed no significant difference from patients who didn't take HU (group 2). However, there are no evidences about the role of HU in improvement of PFTs, but in general few publications have indicated to the impact of HU in reducing the pulmonary complications in patients with SCA ,despite to what was reported that HU therapy might decrease the mortality in adults patients with SCA and the long-term therapy with HU tends to decrease possibility of deaths that caused by pulmonary complications of SCA [30].A case study has found that pulmonary function testing developed a restrictive disorder with a decrease in the diffusion capacity. A Concern was expressed about a cardiac aetiology as opposed to pulmonary damage brought on by hydroxyurea [31]. The current study revealed that hydroxyurea didn't cause any change in pulmonary function tests in SCA patients on 15 mg/kg/day dose. However, further studies are required to investigate the role of the treatment in different doses higher than that we depended in the current study.

Regarding haematological profile, we found opposite findings to that of PFTs in SCA patients on HU. Haematological indicators revealed significant positive changes in patients on HU. WBC, lymphocytes, monocytes and neutrophils were significantly decreased, while RBC, HGB and MCV were significantly increased, in group 3. As it was well established that beside inducing HbF, the cytotoxic effects of HU also decrease marrow production of neutrophils, reticulocytes and other inflammatory cells, which is a remarkable feature of the medication. Decreasing the WBC in SCA patients is of potential therapeutic effect because an elevated WBC has been linked to morbidity and mortality of SCA [32]. Through vascular adhesion, neutrophils and reticulocytes contribute to vasoocclusion; HU decreases their absolute numbers and the surface expression of adhesion receptors. In fact, HU is well tolerated drug of few short-term toxicity. Mild and reversible cytopenia are among the most frequent short-term toxicities including mild to neutropenia, followed by reticulo-cytopenia then thrombocytopenia [30].

Along with the reduction of WBC, neutrophils and lymphocytes, the present study reported significant increases in Hb and RBC. The medical advantage of HU is related to improvement the laboratory findings such as elevations in haemoglobin concentration, MCV and HbF levels, as well as decreases in WBC count in general and neutrophils in particular, reticulocyte count and haemolysis measurements through an improvement hydration of erythrocytes and reduction of sickling. These medical advantages beside other mechanisms including nitric oxide release, vasodilatation and improvement of vascular response have made HU to be the first clinical application of treatment in SCA [33]. A prior study has also showed that HU therapy decreased the incidence of acute chest syndrome, the need for blood transfusions and the number of hospital stays [34]. Furthermore, cohort studies have showed a correlation between HU therapy and the increase in survival rate [35, 36].

## Conclusions

Although HU therapy in a dose 15mg/kg *per* day has contributed to improve haematological profile of patients with sickle cell anaemia, and accordingly it has succeeded

in improving their lives and reducing anaemia, at the same time, it has not been proven to have any positive effect on the functions of the respiratory system, despite what was previously proven to be effective in reducing respiratory complications caused by the disease. Accordingly, due to the importance of the subject of the study, it needs further investigation to prove the reality of the effect of HU in the respiratory system through an extensive study with large numbers of patients and different doses of the treatment.

## Conflict of interest

The authors declare no conflict of interest.

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