

## Impact of temporary and involuntary suppression of hydroxyurea treatment on hematological and clinical parameters in patients with sickle cell disease

Impacto da supressão temporária e involuntária do tratamento com hidroxiureia em parâmetros hematológicos e clínicos em pacientes com doença

Impacto de la supresión temporal e involuntaria del tratamiento con hidroxiurea en parámetros hematológicos y clínicos en pacientes con enfermedad de células

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### Abstract

**Objective:** Here we investigate the impact of involuntary and temporary interruption of hydroxyurea (HU) treatment in patients with Sickle Cell Disease (SCD). **Methods:** Clinical and hematological parameters were explored in 30 patients with SCD under treatment with HU. The study was performed in two different periods: 1 - During nine months of involuntary discontinuation (April/2015 to January/2016) and 2 - During nine months after resumption of the treatment (March/2016 to December/2016). **Results:** The resumption of HU treatment improved the hematological parameters, by increasing levels of hemoglobin ( $+0.65 \pm 0.71$ ), hematocrit ( $+1.16 \pm 2.26$ ), mean corpuscular volume ( $+8.33 \pm 5.89$ ), mean corpuscular hemoglobin ( $+3.15 \pm 2.65$ ). There was a reduction in red blood cell distribution width ( $-0.66 \pm 1.69$ ), reticulocytes ( $-2.53 \pm 1.96$ ), leukocytes ( $-1122 \pm 2764$ ) and platelets numbers ( $-79.933 \pm 162.756$ ). These was followed by a reduction in hospital admissions ( $-0.30 \pm 0.79$ ) and in the number of pain episodes ( $-0.97 \pm 1.19$ ), whereas the denial in episodes of pain crisis increased ( $+1.43 \pm 1.43$ ). After resumption, in period 2, hemoglobin levels were inversely correlated with blood transfusion numbers ( $p=0.034$ ) and acute thoracic syndrome ( $p=0.017$ ). The hematocrit was inversely correlated with the number of consultations ( $p=0.030$ ) and the number of times patients denied crisis ( $p=0.002$ ). **Conclusions:** Our study shows that the treatment with HU improves clinical and haematological parameters in patients and highlights the negative effects of the discontinuation of the treatment in the quality of life in patients with SCD.

**Keywords:** Hydroxyurea; Sickle cell disease; Therapeutic adherence.

## Resumo

**Objetivo:** Neste estudo, investigamos o impacto da interrupção involuntária e temporária do tratamento com hidroxiureia (HU) em pacientes com doença falciforme (DF). **Métodos:** Parâmetros clínicos e hematológicos foram explorados em 30 pacientes com DF em tratamento com HU. O estudo foi realizado em dois períodos distintos: 1 - Durante nove meses de interrupção involuntária (abril/2015 a janeiro/2016) e 2 - Durante nove meses após a retomada do tratamento (março/2016 a dezembro/2016). **Resultados:** A retomada do tratamento com HU melhorou os parâmetros hematológicos, aumentando os níveis de hemoglobina (+0,65±0,71), hematócrito (+1,16±2,26), volume corpuscular médio (+8,33±5,89) e hemoglobina corpuscular média (+3,15±2,65). Houve uma redução na amplitude de distribuição dos glóbulos vermelhos (-0,66±1,69), reticulócitos (-2,53±1,96), leucócitos (-1122±2764) e plaquetas (-79.933±162.756). Isso foi seguido por uma redução nas internações hospitalares (-0,30±0,79) e no número de episódios de dor (-0,97±1,19), enquanto a negação de episódios de crise de dor aumentou (+1,43±1,43). Após a retomada, no período 2, os níveis de hemoglobina foram inversamente correlacionados com o número de transfusões sanguíneas (p=0,034) e síndrome torácica aguda (p=0,017). O hematócrito foi inversamente correlacionado com o número de consultas (p=0,030) e o número de vezes que os pacientes negaram crises (p=0,002). **Conclusões:** Nosso estudo mostra que o tratamento com HU melhora os parâmetros clínicos e hematológicos em pacientes e destaca os efeitos negativos da interrupção do tratamento na qualidade de vida de pacientes com DF.

**Palavras-chave:** Hidroxiureia; Doença falciforme; Adesão terapêutica.

## Resumen

**Objetivo:** En este estudio, investigamos el impacto de la interrupción involuntaria y temporal del tratamiento con hidroxiurea (HU) en pacientes con enfermedad de células falciformes (ECF). **Métodos:** Se exploraron parámetros clínicos y hematológicos en 30 pacientes con ECF bajo tratamiento con HU. El estudio se realizó en dos períodos diferentes: 1 - Durante nueve meses de interrupción involuntaria (abril/2015 a enero/2016) y 2 - Durante nueve meses después de la reanudación del tratamiento (marzo/2016 a diciembre/2016). **Resultados:** La reanudación del tratamiento con HU mejoró los parámetros hematológicos, aumentando los niveles de hemoglobina (+0,65±0,71), hematocrito (+1,16±2,26), volumen corpuscular medio (+8,33±5,89) y hemoglobina corpuscular media (+3,15±2,65). Hubo una reducción en la amplitud de distribución de los glóbulos rojos (-0,66±1,69), reticulocitos (-2,53±1,96), leucocitos (-1122±2764) y recuento de plaquetas (-79.933±162.756). Esto fue seguido por una reducción en las hospitalizaciones (-0,30±0,79) y en el número de episodios de dolor (-0,97±1,19), mientras que la negación en los episodios de crisis de dolor aumentó (+1,43±1,43). Después de la reanudación, en el período 2, los niveles de hemoglobina se correlacionaron inversamente con el número de transfusiones sanguíneas (p=0,034) y la síndrome torácica aguda (p=0,017). El hematocrito se correlacionó inversamente con el número de consultas (p=0,030) y el número de veces que los pacientes negaron crisis (p=0,002). **Conclusiones:** Nuestro estudio muestra que el tratamiento con HU mejora los parámetros clínicos y hematológicos en los pacientes y destaca los efectos negativos de la interrupción del tratamiento en la calidad de vida de los pacientes con ECF.

**Palabras clave:** Hidroxiurea; Enfermedad de células falciformes; Adherencia terapéutica.

## 1. Introduction

Sickle cell diseases encompass a group of disease that affect hemoglobin quality that are inherited in different genotypes (Carneiro et al., 2016.; Bernarde et al., 2021). In these diseases, the concentration of hemoglobin S (HbS is more than 50%). The most relevant manifestation and prevalent form is the homozygosis for the HbS gene or sickle cell disease associated with clinical and hematological complications, culminating in systemic damage since childhood (Bernarde et al., 2021). Subjects with sickle cell disease suffer with several and heterogeneous clinical disorders, varying from severe hemolytic anemia to painful crisis as well as different vascular phenomena (Arduini et al., 2017; Moraes et al., 2022).

Although hydroxyurea is considered an essential drug for the treatment of children and adults with hemoglobin disorders as per the World Health Organization (WHO), the national and international market have gone through periods of shortage since 2011 (World Health Organization, 2017).

In Brazil, patients with sickle cell disease face HU absence in the Universal Health System. However, there is still a paucity information about clinical and hematological manifestations following the same population with sickle cell disease when the HU is suspended. Here, clinical and hematological parameters are compared when HU treatment was involuntarily or temporarily interrupted, from abril/2015 to january/2016, in patients with sickle cell disease followed-up in the ambulatory of hemoglobin pathologies of the Regional Hematology Center in Sobral, Ceará, Brazil.

The primary objective of this study is to assess the impact of the involuntary or temporary interruption of hydroxyurea

(HU) treatment on clinical and hematological parameters in patients with sickle cell disease. Specifically, we aim to analyze the changes in hematological parameters, frequency of clinical events, and hospitalizations during the interruption and after the resumption of HU treatment. This research aims to contribute valuable insights into the consequences of HU shortage and emphasize the importance of consistent access to this essential medication for patients with sickle cell disease.

## 2. Methodology

A comparative and retrospective analysis was performed, as described by Pereira et al. (Pereira et al., 2018), by using the information obtained from medical records from the Regional Hematology Center of Sobral (Hemoce/Sobral), Ceará, Brazil. Approved by the Local Ethics Committee under the protocol number 2.102.863. The study included a sample of 30 patients of both genders diagnosed with sickle cell anemia on therapeutic use of hydroxyurea who had discontinued treatment from April 2015 to January 2016. Patients with sickle cell anemia who started treatment after January 2015 were not included in the study. One death episode accounted for the exclusion of one subject in July/2015 due to complications after HU suspension.

A standardized form for data collection was used to gather information from the medical records. All data collected refer to the period from April/2015 – December/2016. The data collection instrument had three sections: 1<sup>st</sup> part – general information and epidemiological such as gender, race, educational level, profession, age, age of diagnosis, age of HU treatment commencement, and address; 2<sup>nd</sup> part – comparison of hematological parameters: total red blood cells count, hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (HbCM), red blood cell distribution width (RDW), reticulocytes, leukocytes, platelets, sickle hemoglobin (HbS), fetal hemoglobin (HbF), and O<sub>2</sub> saturation; 3<sup>rd</sup> part – general information on the disease, symptoms related to HU treatment discontinuation such as painful crisis, infections, priapism, acute thoracic crisis, hospital admission numbers, and blood transfusions.

The obtained data were exported to the software Statistical Package for the Social Sciences (SPSS) version 20.0 in which analyses were carried out considering a confidence level of 95%. Quantitative data were expressed as means and standard deviation, subjected to normality test Kolmogorov-Smirnov and then analyzed by paired t-test for parametric data or Wilcoxon non-parametric data. Categorical data were expressed as absolute or percentage frequencies and analyzed by McNemar test. Additionally, Spearman correlation was used for clinical and hematological parameters. The significance level was set at  $p < 0.05$  for all analyses.

## 3. Results

Hematologic and clinical parameters were acquired in two different periods for all the participants: Period 1- During nine months of involuntary interruption of the hydroxyurea treatment (April 2015 to January 2016); and Period 2 – when they returned to the treatment with hydroxyurea (March 2016 to December 2016).

Twenty-five (83%) of the subjects in this study were in the age range of 11 to 40 years old, and their average age was  $22.33 \pm 10.01$  years. Although these subjects received the diagnose of sickle cell anemia when they were  $9.05 \pm 7.17$  years old, they only started their treatment around  $18.63 \pm 9.1$  years old on average. Ten (34%) of the subjects were from Sobral, Ceará, Brazil, whereas the 20 others (66%) were from other areas of the north of state of Ceara. Regarding the occupation of the subjects in the study, 15 (50%) were students, 7 (23%) unemployed, and 8 (27%) worked in informal jobs.

The treatment with hydroxyurea markedly increased the levels of hemoglobin ( $+0.65 \pm 0.71$ ,  $p < 0.001$ ), hematocrit ( $+1.16 \pm 2.26$ ,  $p = 0.009$ ), mean corpuscular volume ( $+8.33 \pm 5.89$ ,  $p < 0.001$ ), and hemoglobin mean corpuscular volume ( $+3.15 \pm 2.65$ ,  $p < 0.001$ ). These results were followed by a significant reduction in the red cell distribution width, ( $-0.66 \pm 1.69$ ,  $p = 0.041$ ), reticulocytes ( $-2.53 \pm 1.96$ ,  $p < 0.001$ ), and platelets ( $-79933 \pm 162756$ ,  $p = 0.012$ ), and leukocytes ( $-1122 \pm 2764$ ,  $p = 0.034$ ). Similar findings were obtained for red blood cells ( $-0.07 \pm 0.21$ ,  $p = 0.089$ ) and in the levels of fetal hemoglobin ( $p = 0.195$ ), oxygen

saturation (p= 0.428), and sickle cell hemoglobin (p=0.591) (Table 1).

**Table 1** - Comparison of hematological parameters of subjects with sickle cell disease treated in the Regional Hematology Center of Sobral evaluated in two periods: with and without hydroxyurea.

	Period 1	Period 2	p-Value	Δ
<b>Hematological parameters</b>				
Red blood cells	2.60±0.55	2.54±0.49	0.089	-0.07±0.21
Hemoglobin	8.24±1.32	8.89±1.17	<0.001	+0.65±0.71
Hematocrit	24.65±4.05	25.81±3.56	0.009	+1.16±2.26
MCV	95.67±9.49	104.00±10.31	<0.001	+8.33±5.89
MCHb	32.62±3.94	35.77±4.15	<0.001	+3.15±2.65
RDW	19.04±2.86	18.39±2.47	0.041	-0.66±1.69
Reticulocytes	10.04±2.76	7.51±2.23	<0.001	-2.53±1.96
Leukocytes	11532±3476	10409±2894	0.034	-1122±2764
Platelets	390529±107505	310595±170206	0.012	-79933±162756
Fetal Hb	11.38±6.75	12.14±7.35	0.195	+0.76±3.14
O <sub>2</sub> saturation	93.90±6.90	95.33±6.68	0.428	+1.43±9.77
Sickle Hb	81.41±7.70	80.89±7.62	0.591	-0.52±5.20

\*p<0.05 paired t-test (mean ± SD). Period 1 – nine months of involuntary interruption of the HU treatment (April/2015 to January/2016). Period 2 – after restarting the HU treatment (March/2016 to December/2016). MCV: mean corpuscular volume. MCHb: mean corpuscular hemoglobin. RDW: Red blood cell distribution width. Hb: hemoglobin. Source: Authors (2018).

After the beginning of the treatment, a significant reduction in the number of hospitalizations (-0.30±0.79, p=0.048) was observed. Moreover, treated patients referred less pain crisis (0.97±1.19, p=0.001). The frequency of pain reduced significantly from Period 1 (no treatment - 77%) to Period 2 (treatment - 26%) (p<0.001) (Table 2).

**Table 2** - Comparison of clinical parameters of subjects with sickle cell disease treated in the Regional Hematology Center of Sobral evaluated in two periods: with and without hydroxyurea.

	Period 1	Period 2	p-Value*	Δ	Period 1	Period 2	p-Value <sup>†</sup>
<b>Clinical Parameters</b>							
Consultations	3.23±1.50	3.43±1.70	0.631	+0.20±1.45	30 (100%)	30 (100%)	1.000
Blood transfusion	0.93±1.53	0.53±1.20	0.071	-0.40±1.19	11 (37%)	7 (23%)	0.219
Hospital admission	0.43±0.68	0.13±0.35	0.048	-0.30±0.79	10 (33%)	4 (13%)	0.146
Pain crisis	1.30±1.02	0.33±0.61	0.001	-0.97±1.19	23 (77%)	8 (26%)	<0.001
Denial of pain crisis	1.10±0.88	2.53±1.28	<0.001	+1.43±1.43	21 (70%)	30 (100%)	1.000
Infections	0.23±0.57	0.23±0.63	1.000	-0.00±0.53	5 (17%)	5 (17%)	1.000
Weakness	0.17±0.53	0.07±0.25	0.334	-0.10±0.61	3 (10%)	2 (7%)	1.000
Ulcers	0.10±0.40	0.03±0.18	0.317	-0.07±0.37	2 (7%)	1 (3%)	1.000
Acute thoracic syndrome	0.40±0.77	0.17±0.38	0.107	-0.23±0.77	8 (27%)	5 (17%)	0.453
Priapism	0.10±0.40	0.03±0.18	0.157	-0.07±0.25	2 (7%)	1 (3%)	1.000
Biliary lithiasis	0.10±0.40	0.00±0.00	0.180	-0.10±0.40	2 (7%)	0 (0%)	1.000

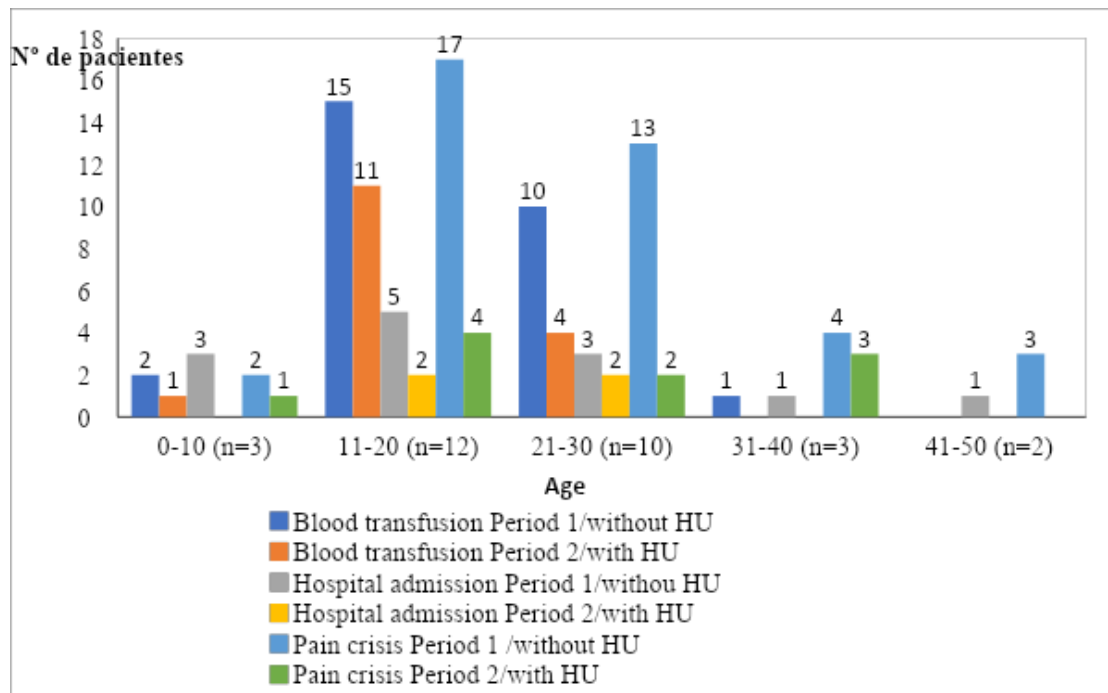
\*p<0.05 Wilcoxon test (mean ± SD); <sup>†</sup>p<0.05 McNemar test (n, %). Period 1 – nine months of involuntary interruption of the HU treatment (April/2015 to January/2016). Period 2 – after restarting the HU treatment (March/2016 to December/2016). Source: Authors (2018).

In the subjects with discontinued treatment, the average number of red blood cells was inversely correlated with the number of blood transfusions ( $p=0.027$ ,  $r=-0.405$ ). The levels of hemoglobin and hematocrit were inversely correlated with the average number of medical appointments ( $p=0.006$ ,  $r=-0.491$  and  $p=0.007$ ,  $r=-0.479$ ), blood transfusions ( $p<0.001$ ,  $r=-0.625$  and  $p<0.001$ ,  $r=-0.615$ ), ulcerations ( $p=0.035$ ,  $r=-0.387$  and  $p=0.028$ ,  $r=-0.402$ ) e priapism ( $p=0.029$ ,  $r=-0.400$  and  $p=0.022$ ,  $r=-0.416$ ). The mean corpuscular hemoglobin volume exhibited a direct correlation with the amount of crisis of thoracic acute syndrome ( $p=0.039$ ,  $r=0.379$ ). The platelets count was inversely correlated with the number of medical appointments ( $p=0.010$ ;  $r=0.460$ ), blood transfusions ( $p=0.005$ ,  $r=0.500$ ), and a number of times when the patient referred weakness ( $p=0.034$ ,  $r=0.388$ ). The fetal hemoglobin values were inversely correlated with the number of medical appointments ( $p=0.027$ ,  $r=-0.404$ ), while the oxygen saturation was directly correlated with the pain levels ( $p=0.049$ ,  $r=0.363$ ).

After return to treatment with hydroxyurea, the number of red blood cells demonstrated negative correlation with the number of times in which the patient referred frailty ( $p=0.022$ ,  $r=-0.417$ ). The hemoglobin levels were inversely correlated to the number of blood transfusions ( $p=0.034$ ,  $r=-0.389$ ) and acute thoracic syndrome. The reticulocytes numbers were inversely correlated with the times when the patient reported frailty ( $p=0.028$ ,  $r=-0.402$ ). The platelets were directly correlated with the number of blood transfusions ( $p=0.024$ ,  $r=0.411$ ), and the oxygen saturation was directly correlated to the number of times in which the patients denied the crisis ( $p=0.030$ ,  $r=0.396$ ).

We also observed that the clinical parameters increased with the age of the subjects, although no statistical significance was observed. It was observed an increase in allergic crisis, blood transfusions, and in the number of hospitalizations in those patients aging from 11 to 30 years old (Figure 1).

**Figure 1** - Clinical parameters correlation (number of blood transfusions vs number of hospital admissions vs number of pain crisis) and age of patients with sickle cell disease under follow-up in the regional hematology center of Sobral evaluated in two periods: with and without hydroxyurea treatment (n=30).



Source: Authors (2018).

#### 4. Discussion

A peculiar factor about our investigation is the fact that clinical and hematologic parameters of patients under

hydroxyurea were compared in two different moments: Period 1 – nine months of involuntary interruption of the treatment with hydroxyurea (April 2015 to January 2016); and Period 2 – nine months after the reinstatement of the treatment with hydroxyurea (March 2016 to December 2016).

Hydroxyurea is used in the treatment of cancer and hematologic diseases. Even though the World Health Organization considers it an essential tool in the treatment of children and adults with hemoglobinopathies since 2011 the Brazilian market and the international market have been undergoing a shortage of this drug (World Health Organization, 2017). Clinical studies have demonstrated the efficacy of hydroxyurea in the treatment for sickle cell anemia in adults (Bandeira, 2020; Gardner et al., 2016) and promising results in children (Silva et al., 2022; Ware et al., 2017; Ware et al., 2016; Bernaudin et al., 2016) since October 2015, the supply of hydroxyurea has been impaired. The number of deaths due to the interruption of the treatment is crescent (Bandeira, 2020).

The continuous treatment with hydroxyurea presents advantages to the sickle cell disease patients, such as the induction of fetal hemoglobin synthesis. The cytotoxic effects of the hydroxyurea cause a reduction in the number of total leukocytes, reticulocytes, and platelets, which are important inflammatory mediators (Arcanjo, 2018; Silva et al., 2021). Regarding the behavior of the hematologic parameters, it was observed an increase in the average levels of hemoglobin, hematocrit, mean corpuscular volume, and mean hemoglobin corpuscular volume. On the other hand, it was seen a significant decrease in the red cell distribution width, number of reticulocytes, leukocytes and platelets. Both neutrophils and reticulocytes promote obstruction of the blood vessels through cell adhesion. The hydroxyurea reduces the absolute number of these type of cells, hindering the expression of adhesion receptors (Platt et al., 1994; Rhiannon & Hurwitz, 2018).

In 1997, Steinberg and colleagues demonstrated that the increase of fetal hemoglobin is a response to the treatment with hydroxyurea (Steinberg et al., 1997). Clinical data showed an increase in the levels of fetal hemoglobin in patients with sickle cell disease as a response to the treatment with hydroxyurea when compared to patients not treated with the same medication (Moreira, 2022; Ballas et al., 2010). Similar finding were obtained in hematologic tests of European children with sickle cell disease treated with hydroxyurea (Montalembert et al., 2016).

The clinical manifestations observed in patients of our study changed in the two periods of the investigation. During period 1, higher rates of pain crisis, blood transfusions, and hospitalizations were observed. In this period, hydroxyurea was suspended, and 11 patients underwent blood transfusions, 4 patients needed to stay in the hospital. In period 2, when the patients resumed the hydroxyurea therapy, only 7 blood transfusions and 4 hospitalizations were registered. After resuming the HU treatment, a significant decrease in the hospitalizations, pain crises, and a rise in the amount of pain crisis denial.

The number of consultations, transfusions, infections, weakness episodes, ulcers, acute thoracic syndrome, and biliary lithiasis did not vary significantly. The frequency of pain crisis significantly reduced from period 1, without treatment (77%), to period 2, with treatment (26%). Evaluating these two periods, it shows clearly how harmful and life threatening the interruption in the treatment can be to the patients. Additionally, in an economically point of view, these events leads to unnecessary money spent and all of these could be avoided just by a more approachable public health system in order to reduce the shortage of hydroxyurea in the centers for drug distribution.

Santana and colleagues, 2017 observed that algic crisis in 42% of patients was the most common reason for hospitalization (Santana et al., 2017). In 2015, Zambon reported that common complications of the sickle cell disease are an algic crisis or acute vaso-occlusive crisis. A sickle cell disease painful crisis is defined as the resulting ischemia of tissues caused by occlusion of vessels commonly in the bone marrow and bones. The vaso-occlusive crisis is an acute complication that most traumatize patients as it manifests as an acute pain crisis.

Typically, these crises are of excruciating course and sudden onset, but some patients experience a gradual episode of pain. Almost all affected individuals will present an acute pain crisis episode over their lifetime, often they happen with no



prodromes and dampen the quality of life (Sousa et al., 2020).

Here, we demonstrate that the most common cause of hospitalization is the vaso-occlusive crisis. In 2015, Vikari and colleagues showed that the use of HU halved the number of such crises as well as reduced the need for blood cell transfusions (Vicari et al., 2015). By reducing the frequency of crisis, these patients do not need to be hospitalized, which improves their quality of life and attenuates the global treatment costs. In 2017, Martins and Teixeira analyzed 8,103 hospital admissions during 2008-2014 in the State of Bahia. Ninety-six percent of these cases needed an urgent medical assessment due to a vaso-occlusive crisis (Martins & Teixeira, 2017).

It is interesting to highlight that the clinical manifestations were much more present in patients ranging from 11 to 30 years old, who most received blood transfusions, hospitalizations and clinical occurrence of pain crises, acute thoracic syndrome, infections, the flu, ulcers, priapism in both periods of the study. This demonstrates that the clinical state of patients with sickle cell disease can be correlated with age. However, such correlation did not present significant results. Other results evidenced a vast predominance of children and adolescents from 1 to 14 years old presenting many complications (Martins & Teixeira, 2017), while Felix and colleagues in 2010 demonstrated a higher prevalence of young individuals ranging from 18 to 30 years old (Nevitt et al., 2017).

The clinical evolution of the sickle cell disease which characterizes itself as acute complications that afflict different age ranges and accounts for urgent hospital admissions (Souza & Geron, 2019).

The vaso-occlusive crisis is the most common cause of hospitalization and is not preventable, except when hydroxyurea treatment can reduce the frequency of crisis (Joep et al., 2017). The treatment with HU improves clinical and haematological parameters in patients and highlights the negative effects of the discontinuation of the treatment in the quality of life in patients with SCD (Souza & Geron, 2019; Joep et al., 2017).

## 5. Conclusion

In summary, the adherence to hydroxyurea treatment is a multi-factorial process that is influenced by patient perceptions about hydroxyurea, severity of the disease, and on top of these, the treatment has a major influence by the economic status of the population. Our study shows that a temporary suppression of the hydroxyurea treatment was associated with increased hematological and clinical symptoms, hospitalizations, requirement for blood transfusion and death. These have a severe impact in the quality of life of the patients and it is a life threatened to the patients.

It is a common sense that the sickle cell disease is already a severe condition with constant suffer to the patients. Therefore, a more approachable public health system, in which the hydroxyurea distribution was more frequent would reduce the costs with hospitalization and would to improve the quality of life of patients with sickle cell disease. Although this is a local center, results obtained with this study can be extrapolated to a bigger population and other health centers that face similar problems.

Suggestions for future work include expanding the study to a broader sample and evaluating other healthcare centers facing similar challenges. Additionally, investigations into strategies to enhance treatment adherence, even under conditions of drug scarcity, can provide valuable insights. The ongoing research in this field is crucial to ensuring the well-being of patients with sickle cell disease and informing health policies aimed at improving access to essential treatments.

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