

# Acute Events in Hospitalized Patients with Sickle Cell Anemia before and after the Use of Hydroxyurea

ORIGINAL

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## Abstract

**Objective:** To estimate the occurrence of acute events in hospitalized patients with sickle cell anemia (SCA) before and after the use of hydroxyurea (HU).

**Method:** The study has a quantitative approach, of analytical cohort type developed in two public referral hospitals in the Midwest region of Brazil, from November 2010 to October 2011. Data collection was performed on records of patients diagnosed with SCA. The interval time for the data collection was 30 years, which corresponded between 1980 and 2010. The research was approved by the Ethics Committee of the Federal University of Mato Grosso do Sul, Campo Grande/MS, Brazil, under protocol 1822/2010.

**Results:** The sample had 32 medical records of hospitalized patients diagnosed with SCA who used HU. The mean age of the participants was  $25.65 \pm 11.92$ ; the average time of drug exposure was  $6.0 \pm 2.8$  years; the average initial dose was  $17.00 \pm 5.3$  mg/kg/day and final dose of  $22.10 \pm 5.3$  mg/kg/day. After using HU, the fetal hemoglobin ranged from  $8.41 \pm 0.95$  to  $14.44 \pm 13.7\%$  ( $p < 0.001$ ). There was a reduction of the average leucocyte, absolute neutrophil, acute events, total infections and blood transfusions.

**Conclusion:** The effects of HU exposure caused an increase in fetal hemoglobin level, decreasing leukocyte, absolute neutrophils and acute events, transfusions and hospitalizations by the use of non-opioid.

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## Keywords

Sickle Cell Anemia;  
Hydroxyurea; Infection.

## Introduction

Sickle cell anemia (SCA) is a genetic disorder caused by the homozygous of gene  $\beta^S$  encoding the hemoglobin S (HbS). The HbS results from the substitution of glutamic acid (GAG) by valine (GTG) at position six of the globin  $\beta$  chain. This exchange results in profound changes in the physicochemical properties of the molecule of hemoglobin (Hb) when deoxygenated [1, 2]. Such changes occur in cell morphology, and the RBCs are an elongate form known as "sickle erythrocyte" altering the rheology of red blood cells and the erythrocyte membrane and results in the polymerization phenomenon [3, 4]. These changes culminate in two important pathophysiological processes of sickle cell anemia, hemolysis, and vase-occlusion [5].

The occurrence of the vase-occlusive episode is the pathophysiological event decisive for the origin of most of the signs and symptoms of the clinical picture of patients with SCA and other manifestations or acute events that are worth mentioning, as the painful crises, aplastic, hemolytic, pulmonary complications, neurological and hepatobiliary as well as infections [6, 7]. From these events, the pain crisis is considered the most dramatic event in the picture of the disease [8].

The polymerization phenomenon is regulated by the level of HbS and decreasing with the presence of other forms of hemoglobin that does not contain mutant forms of the  $\beta$  globin. The main therapeutic approach to SCA is trying to change the production of hemoglobin S for fetal hemoglobin (HbF), resulting in a less severe degree of symptoms and less hemolytic anemia [9]. For cases with an indication, the treatment with hydroxyurea (HU) may be instituted to ameliorate the clinical picture of the disease [10].

By its action, the HU elevates HbF and consequently decreases the vase-occlusion and hemolysis, resulting in the reduction of the frequency of transfusions, painful events, number, and duration of hospitalization. This treatment further enhances

the hematological parameters and increases nitric oxide concentrations, depending on the inhibitory role of HbS polymerization [11]. The effective therapeutic action is observed in observational studies [12] and demonstrated in Randomized Clinical Trial (RCT) with serious adults [13].

The benefits of using HU found that early drug exposure to the patient brings a greater likelihood of mortality prevention [14]. Given the above, this study aimed to estimate the occurrence of acute events in hospitalized patients with sickle cell anemia before and after the use of hydroxyurea as a treatment option.

## Method

This is a study with a quantitative approach, of the analytical cohort type developed in two public referral hospitals in the Midwest Brazil, from November 2010 to October 2011.

Data collection was performed on records of patients diagnosed with sickle cell anemia (HbSS). The interval time for the data collection was 30 years, which corresponded between 1980 and 2010. Patients with at least 24 hours of hospitalization, with a diagnosis of sickle cell anemia confirmed by hemoglobin electrophoresis and having a medical indication for HU treatment were included.

The hematological variables collected were: fetal hemoglobin (HbF); total hemoglobin concentration; hematocrit; erythrocytes or RBCs; leukocytes, absolute neutrophils, and platelets, collected before and after the HU use. The evaluation of laboratory parameters in this study followed the values espoused by Failace [15] Falcão and Calado [16]. The absolute number of neutrophils is the total of neutrophils about leukocytes [15], calculated using the formula: absolute neutrophil = neutrophils x leukocytes/100.

The clinical variables collected were: hydroxyurea (starting date, age at the beginning of the treatment, initial dose, final dose and average ex-

posure time) and acute events before and after the use of HU (pain crises, acute chest syndrome/pneumonias - STA/pneumonias), infections, sepsis, priapism, stroke, cholelithiasis, aplastic crisis and the number of blood transfusions). Other variables were related to hospitalizations using opioid analgesics, non-opioid analgesics.

The acute events were defined according to criteria established by the Ministry of Health of Brazil. [17] In the variable of acute events, all events were included, including pain crisis. It was opted for this study to analyze the frequency of painful crisis as an independent variable separately. Moreover, in the variable infections, all infections are included in general, including pneumonia. It was also decided to examine separately pneumonia to be more frequent infections in sickle cell disease.

For the relationship of individualized mg/kg to the HU dosage, the data on the weight of each patient and the prescribed dose recorded in the medical record were used, both before and after use.

When analyzing the results, the comparison between the moments before and after the use of HU was performed using the Wilcoxon test when the samples did not pass the normality test, or through the t Student test when they passed the normality test. The other results of the variables evaluated in this study were presented in descriptive statistics. The statistical program used was SigmaStat, version 3.5 and the level of significance was  $p < 0.05$ .

The study was previously evaluated and approved in its ethical, and methodological aspects by the Ethics Committee in Research of the Federal University of Mato Grosso do Sul, Campo Grande/MS, Brazil, under protocol 1822/2010.

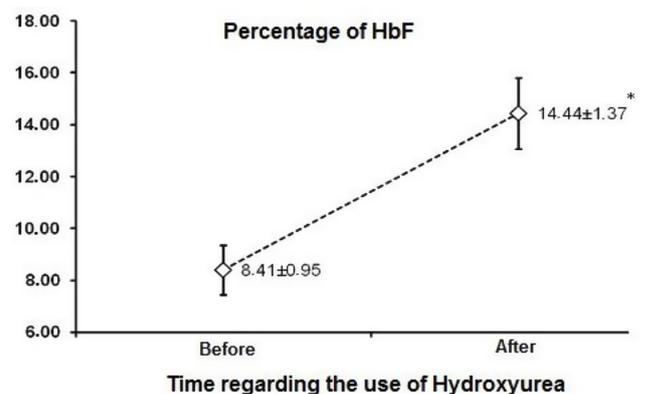
## Results

The sample was 32 medical records of hospitalized patients diagnosed with SCA who used HU. The mean age of subjects was  $25.65 \pm 11.92$ , which in-

dicates that most of the patients were in the third decade of life. The average time of exposure to drug was  $6.0 \pm 2.8$  years, and the mean initial dose was  $17.00 \pm 5.3 \text{ mg/kg/day}$ , and the final dose was  $22,10 \pm 5.3 \text{ mg/kg/day}$ .

Figure 1 shows the percentage of HbF level reached in this sample after using HU. This result demonstrates the effectiveness of the drug, which resulted in a significant increase in HbF ( $p < 0.001$ ).

**Figure 1:** Fetal hemoglobin percentage (HbF) in patients with sickle cell anemia before and after the use of hydroxyurea.



\*: Significant difference from the time before using hydroxyurea (t Student test,  $p < 0,001$ ).

The leukocytes showed a significant reduction in the use of hydroxyurea (Table 1).

**Table 1.** Hematological parameters in patients with sickle cell anemia before and after the use of hydroxyurea between 1980 and 2010. Campo Grande/MS, Brazil, 2016 (n=32).

Variable	Time regarding the use of hydroxyurea		P-value
	Before <sup>1</sup>	After <sup>1</sup>	
Hemoglobin (g/dL)	8.08 ± 0.22	8.04 ± 0.22	0.973
Hematocrit (%)	25.30 ± 0.64	24.55 ± 0.66	0.465
Erythrocytes ( $10^6/\mu\text{L}$ )	2.7 ± 78544.01	2.5 ± 77034.80	0.119
Leukocyte ( $10^3/\mu\text{L}$ )	15.986 ± 1044.72	13.984 ± 947.32	0.0422 <sup>2</sup>

Variable	Time regarding the use of hydroxyurea		P-value
	Before <sup>1</sup>	After <sup>1</sup>	
Absolute neutrophil (mL)	11157.32±908.64	10070.20±742.32	0.185
Platelets (10 <sup>3</sup> µL)	277.964.29±21087.34	320.160.00±20842.72	0.278

<sup>1</sup>: Data are presented as mean±standard error of the mean.  
<sup>2</sup>: p-value with a significant difference between the times before and after use of hydroxyurea.

In **Table 2**, there are the results for the mean and standard deviation of clinical variables, normalized to a period of 10 years in hospitalized patients with sickle cell anemia before and after the use of HU. After the drug use, there was a significant reduction in hospitalizations for treatment with non-opioid analgesics in acute events infections, pneumonia and blood transfusions.

**Table 2.** Average number of hospitalizations and acute events (normalized to a period of 10 years) seen in patients with sickle cell anemia before and after the use of hydroxyurea between 1980 and 2010. Campo Grande/MS, Brasil, 2016 (n=32).

Variable (Average every 10 years)	Time regarding the use of hydroxyurea		P-value
	Before <sup>1</sup>	After <sup>1</sup>	
Interactions with non-opioid analgesics	10.65±1.76	6.51±1.29	0.014 <sup>2</sup>
Interactions with opioid analgesics	7.34±1.27	5.27±1.03	0.127
Acute events	14.16±2.62	7.05±1.48	0.014 <sup>2</sup>
Pain crises	8.20±1.47	5.32±1.17	0.264
Infections	1.58±0.52	0.35±0.17	0.005 <sup>2</sup>
Pneumonias	2.80±0.79	0.79±0.36	0.012 <sup>2</sup>
Blood transfusions	20.12±4.56	10.43±2.10	0.037 <sup>2</sup>

<sup>1</sup>: Data are presented as mean±standard error of the mean.  
<sup>2</sup>: p-values significant difference between before and after the use of hydroxyurea (Wilcoxon Test).

## Discussion

After using HU, there was a significant increase in HbF level of 8.41±0.95 to 14.44±1.37%, with

an initial medication dosage of 17mg/kg/day and final dose of 22.10mg/kg/day. The results of this study demonstrated the effectiveness of medicine treatment for SCA. These findings are like those found in an observational study that evaluated the pharmacokinetics, toxicity and HbF production with a sample of 32 HbSS patients. In this study, the mean age ranged from 27.60±6.3 years, but the initial dosage was 10mg/kg/day and ranged up to 35mg/kg/day, as there was a significant increase in HbF of 4±2 to 15±6% after its use, p<0.001 [12].

In adults,  $\gamma$  globin genes have a normal sequence, but remain almost inactive at this stage. However, in exceptional conditions, these genes are activated to produce red blood cells with highly enriched Hb, composed of  $\alpha$  and  $\gamma$  chains called as HbF. The HU acts while acting in  $\gamma$  globin genes from primitive progenitors and it forces the production of F. This process causes cells to change the kinetics of erythroid proliferation, and produces nitric oxide that acts directly in the production of HbF. [9]

The use of HU in patients with sickle cell anemia is the result of research carried out at the end of the 1970s, in which it was demonstrated that the change in vivo of the erythropoiesis kinetic arises from the HU when inducing the production of fetal hemoglobin [18].

Interestingly, erythrocytes, hemoglobin, and hematocrit with averages already reduced before the use of HU did not increase after treatment with the drug. These results differ from those observed in another study which varied dosage of 10mg/kg/day to 35mg/kg/day performed in people with sickle cell disease [12].

In this study, the leukocytosis showed a significant reduction in the use of HU. These findings corroborate the research that highlighted the key role of leukocytes in the oxidative and inflammatory stress process. Accordingly, leukocytosis may occur due to increased levels of cytokines my-

eloid proliferative and delayed apoptotic process [19]. Furthermore, leukocytes play a central role in initiating vase-occlusive event since from these cells there is the aggregation of other blood cells (erythrocytes, platelets) that promote the narrowing of the vessel lumen. This phenomenon affects the circulation and leads to hypoxia. In response, leukocytes will produce cytokines that induce the expression of adhesion molecules by vascular endothelium [20].

The absolute neutrophils showed a small reduction in their average values. In a study of patients diagnosed with SCA residents in the United States and Canada it was found that after two years of therapy with HU, there were half of the patients with an increase in HbF with reduced leukocytes and consequent improvement of the disease in the experimental group [13].

In this study, the acute events showed a significant reduction in the average after the use of HU. The effect of this drug reduces the incidence of vase-occlusive crisis supposedly by elevated HbF, with improvement in patients' symptoms [21]. Evidence of the effect of HU is demonstrated with the explosion of young F cells within 72 hours [22].

The reduction of acute events after the use of HU emphasizes the complexity of the vase-occlusive process in sickle cell anemia, not completely understood condition and participation of neutrophil as the vase-occlusive event initiators. In this sense, polymorphonuclear neutrophils (PMN) are activated by direct interaction sickled erythrocytes (SS-RBC), which takes the PMN to play a crucial role in the cascade of events leading up to the crisis. Therapeutic interventions intended to reduce SS-RBC-PMN [21].

As for the total of acute events in this study, there was a reduction in the use of HU. In a Brazilian study, there was a reduction of three events: painful crises (1.86 to 0.81,  $p=0.0014$ ), acute chest syndrome (from 0.35 to 0.08,  $p=0.0045$ , infections (1.03 to 0.5,  $p=0.047$ ) [23].

In this study, pain crises did not show a significant reduction, but its frequency decreased after using HU. In addition to this event, there was a significant reduction in the mean of transfusions and hospitalizations. These results corroborate an RCT developed with 299 patients, in which there was a reduction in crisis rate in treated patients (mean 2.5 vs. 4.5 crises/year,  $p<0.001$ ) compared to placebo, as well as in transfusions and hospitalizations [13]. A systematic review study aimed at identifying in the literature and gathering the scientific evidence showing effectiveness, barriers, and toxicity of the use of HU in children with SCA, also found reduced pain episodes and hospitalizations [24]. Another review gathered scientific evidence on the management of sickle cell disease, and it strongly recommends the use of hydroxyurea for adults with 3 or more vase-occlusive crises per year, with episodes of pain that interfere with their daily lives. [25]

Regarding the hospitalizations for treatment of acute events with opioid analgesics and non-opioid after using HU, there was an average reduction in the frequency requirements of these analgesics and significant reduction of the use of non-opioids. In the therapeutic approach, morphine is the opioid agonist most widely used for pain control, and meperidine is contraindicated for patients with sickle cell disease, because there may be physical dependence [8].

In infections, there was a significant reduction of the mean values in this study after using HU. In a survey of 43 children with sickle cell anemia (93% asplenia or almost asplenia), the spleen filtering function was measured before and during therapy with maximally tolerated dose of HU and average use of 2.6 years. Of this total, six patients (14%) had the spleen function completely recovered [26]. The spleen in the initial state of hipoesplenia presented reversibility function in response to certain treatments such as hydroxyurea [27].

The most frequent acute event among the infections in the sample studied was pneumonia. To

discuss this finding, it was based on a retrospective study that showed an incidence of 16% of serious bacterial infections, mostly pneumonia being without records in the use of HU [28, 29].

Limitations of this study are related to some variables that were not systematically in the records and prevented them from making some interesting analysis. It is emphasized that these limitations did not prevent achieving the goal of current research.

## Conclusion

The results of this study showed that after the use of hydroxyurea in patients with sickle cell anemia (SCA), there was a significant increase in the level of HbF, significant reduction in mean leukocyte values, absolute neutrophils, as well as in acute events, transfusions and hospitalizations for use non-opioid in the sample investigated. It is suggested to carry out further studies with an experimental approach to find what is the ideal dose of HU to be administered to patients with sickle cell anemia.

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