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Clinical and Biologic Outcomes Following the Administration of Hydroxyurea to Homozygote Sickle Cell Patients in Two Health Facilities of Yaounde

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Authors' contributions

This work was carried out in collaboration between all authors. Author BCC designed the study, wrote the protocol, enrolled, followed up some participants, performed the statistical analysis and wrote the first draft of the manuscript. Authors AVKK and NT enrolled, followed up some participants and verified the analyses of the study. Author ABK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Sickle cell disease is the most frequent genetic disease worldwide with high mortality and morbidity rates. Several therapeutic medications have been put in place amongst which hydroxurea, an antineoplastic for which the clinical-biologic benefits for the patients have been established in several countries. However in our country few studies have been done on the benefits of this drug.
Our objectives were to determine the clinical and biologic responses upon the administration of hydroxyurea to sickle cell patients followed up at the Yaounde Central Hospital and the Frantz

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Fanon medical foundation.
We carried out a descriptive cross sectional study with retrospective and prospective components from January 2017 to June 2017. All homozygote sickle cell patients were included in this study (children and adults).
We enrolled 40 patients. The median age was 22 years with extremes of 4 and 50 years. We found a good clinical response marked by a significant reduction by 68% of the number of vaso occlusive crises (VOC) per year. We also found a good biologic response through a statistically significant increase of 7.35% in the level of hemoglobin F (Hb F). However several patients (40%) had poor compliant to the treatment.

Keywords: Hydroxyurea; sickle cell disease; outcome; clinical; biologic; Yaounde.

1. INTRODUCTION

Sickle cell disease also known as sickle cell anemia is a hemoglobinopathy in which hydrophilic glutamic acid is replaced by hydrophobic valin at position 6 on the beta globin chain. This leads to modifications in the electrophoretic properties of hemoglobin [1].

It the most frequent genetic disorder in the whole world and particularly from people with African origin [2]. According to the World Health Organization (WHO) in 2014 there were about 70-120 million careers of the sickle cell trait in the world: we notice a 312.000 annual births of sickle cell patients with 200.000 in Sub Saharan Africa [3] where the strategy of management in order to reduce the morbidity and mortality is not within reach. This is the reason why this figure will rise to 400.0000 by 2025 [4]. In Cameroon according to *Beyeme* et al. in 2004, the frequency of the S trait was 22.3%, the frequency of homozytote SS was 1.7% according to regions of the country [5]. This is indeed a public health problem which necessitates a multidisciplinary approach.

The management of this disorder has highly evolved with years. It seems to be that several factors: genetic and environmental influences the physiopathology of the disease. It is these factors that current treatments tend to ameliorate. Thus the treatment of sickle cell disease is not just symptomatic; it is oriented towards fundamental treatment of its complications [6]. New therapeutic medications have been put in place especially bone marrow transplants and administration of hydroxyurea.

Hydroxyurea (hydroxycarbamide) is a chemotherapeutic drug synthesized for the first time in 1869 for the reduction of the abnormally high white blood cells in patients with myeloproliferative disorders [7]. Its efficacy in the treatment of homozygote sickle cell disease in adults as well as children is known since 1995.

Several studies have been carried out in the whole world in order to evaluate the efficacy of hydroxyurea on sickle cell patients. These studies found an improvement in the phenotype of the disease [8-10], a reduction of the mortality [11-14]. Hydroxurea is not often used in Africa because it is not accessible (cost, not available in pharmacies),reluctance of health personnel and some parents because of side effects(infertility),meanwhile the clinical and biologic benefits of this drug in severe cases of sickle cell disease have been proven in Africa and Europe.

In Cameroon very few studies have been done, those studies carried out does not include pediatric patients. In 2014, Hassanatou et al. [15] evaluated the efficacy of hydroxyurea in children within 1 year at the Chantal Biya Foundation. They found a clinical and biologic improvement. The introduction of hydroxyurea in the management of sickle cell disease is of recent at the Yaounde Central Hospital but is already a routine at the Frantz Fanon Medical Foundation since 10 years.

We proposed in this study to evaluate the clinical and biologic outcomes of sickle cell patients (children and adults) in the short and long term who are taking hydroxyurea.

2. METHODOLOGY

We carried out a descriptive study with prospective and retrospective components within a 6 months period (January to June 2017). The study site was the hematology service of the Yaounde Central Hospital and the Frantz Fanon Medical foundation of Yaounde.

We enrolled all sickle cell patients without distinction of race or sex that we received at the outpatient consultation and those that were admitted and we treated them with hydroxyurea.

We included in our study: Homozygote sickle cell patients; homozygote sickle cell patients treated with hydroxyurea for at least 3 months.

Were not included in our study: patients receiving other treatments for sickle cell disease besides folic acid and antibioprophylaxy; patients on vasodilators; patients who refused to participate.

We did a consecutive sampling and considered our sample size at the end of sampling. In both the retrospective and prospective components of this study, prior to initiation of HU therapy we collected clinical and biologic information. We entered the information collected in data entry forms and hospital registers.

The retrospective aspect of this study concerned sickle cell patients seen at consultation or admitted or volunteers who were receiving hydroxyurea (HU).

The prospective component concerned patients who were freshly put on HU and who had the following criteria for initiation of HU:high frequency of severe Vaso Occlusive Crises (VOC) or those with at least 3 hospitalizations within 1 year; more than 3 blood transfusions for severe anemia within one year; at least 2 acute chest syndrome per year; past history of cerebrovascular accident or at risk of a cerebrovascular accident; chronic leg ulcer; past history of priapism; organ failure (e.g. heart, lung); connective tissue disorder (Rheumatoid polyarthritits, systemic lupus); patient aged more than 50.

We used CSPRO version 6.0 to enter our data and analyzed them with the IBM SPSS software version 23.0.

Our results were expressed as frequencies for qualitative variables, means and standard deviations for quantitative variables with a symmetric distribution and medians and quartiles for non-symmetric distributions.

The means were compared with the Student T test and qualitative variables were compared with the Mc Nemar-Bowker test. A $p<0,05$ was considered to be statistically significant.

3. RESULTS

In total, 40 patients were enrolled amongst which 17(42.5%) at the Central Hospital of Yaounde (CHY) and 23(57.5%) at the Frantz Fanon Medical Foundation. The most represented age range was the (10-20) year age group (47,5%). The age of the patients varied from 4 to 50 years with mean of 20,30 ± 10,13 years. We had 22 women (55%) and 18 men (45%) with sex ratio of 1.2 in favor of women. The most represented level of education was the secondary level (35%), then the high level (32.5%). Most of the patients were unemployed (52.5%). Their monthly wages were <100.000 in 50% of cases. Most of the patients had no health insurance (77.5%).Most of the patients originated from the Center region (45%) and the West region (27.5%) Table 1.

Ninety percent (90%) of the patients were diagnosed sickle cell before the age of 5; this corresponds to the age of replacement of Fetal Hemoglobin (HbF) by adult hemoglobin. However 3 patients (7.5%) were diagnosed after 10 years of age. Before initiating treatment, 27(67.5%) patients affirmed that they were undergoing regular medical follow-ups. After initiating treatment, 39(97.5%) patients regularly came for consultation. Before initiating treatment, 38 patients (97.5%) were receiving folic acid and after initiation of treatment just one was not taking it.

Table 1. Distribution of patients with respect to level of education, profession, monthly income, matrimonial status and region of origin

Variables	Number (N=40)	Percentage (%)
Level of education		
Non	1	2,5
Primary	12	30,0
Secondary	14	35,0
High	13	32,5
Profession		
Un employed	21	52,5
Private sector	19	47,5
Monthly income		
<100000	20	50,0
>100000	7	17,5
Matrimonial status		
Single	31	77,5
Married	9	22,5
Medical insurance		
Yes	9	22,5
No	31	77,5
Region of origine		
Centre	18	45,0
West	11	27,5
Other*	11	27,5

**South, South-West, East, Littoral, West, Adamaoua, North, Far-Nord*

Antibioprophylaxy was used by children aged less than 12 years old. One patient was receiving morphine for a long period for pains. By the end of 6 months of treatment, the intensity of his pain had subsided at the point that he did not have to take morphine to calm the pains. Eight patients had brothers or sisters who were sicklers and who were also receiving HU. Three patients voluntarily decided to take HU. The duration of treatment varied from 3 to 168 months, with a median of 12 months. 40% of patients were treated on a short term (3 to 8 months) and 60% of patients in the long term (more than 8 months).

There was a marked reduction of the frequency of crises (from 10.83 to 4.31 crises/year); in the duration (4.33 to 2 days) and the intensity (8.2 to 5.63/10) of the vaso-occlusive crises(VOC); a significant decrease in the frequency(3.33 to 1.95) and the duration (6.97 to 4.80 days) of hospital admissions. In contrast the reduction in the number of blood transfusions (from 1.38 to 0.33) was not statistically significant (p=0.120) and in same light as the quantity of blood received (p=0.795). There was no statistically significant difference between the clinical response in the short term and the long term as concerns the characteristics of VOC, hospital admissions and blood transfusions. The occurrence of complications has greatly reduced in patients on treatment. The major acute complication was VOC. 67.5% of patients had VOC before the unset of treatment and after 8 months of treatment; just 50% of patients had VOC. Before the unset of treatment, 6 patients had VOC and after the unset of treatment, just one had a VOC. The major chronic complication was leg ulcers that were present in 17.5% of patients. All these leg ulcers were superficial ulcers. After 8 months of treatment these complications disappeared in these patients (see Tables 2 and 3).

Table 2. Distribution of patients with respect to characteristics of VOC, hospitalizations and blood transfusions in the short term and after initiation of treatment

	Total : N=40		
Variables	**Before HU (n= 40)**	**After HU (n= 24)**	**p value**
	Mean ± SD	**Mean ± SD**	
VOC			
Number	10,83±8,02	3,5±2,64	**<0,001**
Duration	4,33±1,99	2,08±0,83	**<0,001**
Intensity	8,2±0,88	5,63±1,41	**<0,001**
Hospitalisations			
Number	3,33±2,14	0,88±0,85	**<0,001**
Duration	6,97±2,69	5,09±1,81	**<0,001**
Blood transfusion			
Number	1,38±1,55	0,33±0,70	**<0,001**
Quantity	928,57±522	900±223,61	**<0,001**

Table 3. Characteristics of VOC, hospitalizations and blood transfusions before initiation of treatment and in the long term after the initiation of treatment

	Total : N=40		
Variables	**Before HU (n= 40)**	**After HU (n= 24)**	**p value**
	Mean ± SD	**Mean ± SD**	
VOC			
Number	10,83±8,02	3,5±2,64	**<0,001**
Duration	4,33±1,99	2,08±0,83	**<0,001**
Intensity	8,2±0,88	5,63±1,41	**<0,001**
Hospitalisations			
Number	3,33±2,14	0,88±0,85	**<0,001**
Duration	6,97±2,69	5,09±1,81	**<0,001**
Blood transfusion			
Number	1,38±1,55	0,33±0,70	**<0,001**
Quantity	928,57±522	900±223,61	**<0,001**

The biologic response was marked in the short term by: a decrease in the level of HbF (8.19 to 7.99%), an increase in hemoglobin level (7.38 to 8.03), an increase in Mean Cell Volume (MCV) (88.63 to 88.81 Fl), a reduction in the number of leucocytes (14 037 to 11 298/mm3), a reduction in the number of platelets (45 3570 to 44 1500/mm3). The biologic response was marked in the long term by: an increase in HbF (8,19 to 15,54%), an increase in the Hb level (from 7,38 to 8,57g/dL), an increase in MCV (from 88,63 to 94,17fL), a decrease in the number of leucocytes (from 14037 to 10945/mm^3), a decrease in the number of platelets (453570 to 364966/mm^3). The only statistically significant difference between the biologic response in the long term and in the short term was the variation in the HbF level of 8% with p<0,001.All the other variations were not statistically significant.

40% of the patients were not taking their medication every day. 50% of the patients were not taking their medication every day because of the lack of finances and 37.5% because of consequences (fertility, anticancer). Most of the patients did not have any side effects (26%). The blackening of fingers was the most frequent side effect (17.5%).

4. DISCUSSION

The sample size was 40 patients, more than that of d'Hassanatou et al*.* [15] in Cameroon that was 30 patients, or of *Mellouli* in Tunisia [16] that was 27 sickle cell homozygotes or of Singh et al. in India [17]. This difference can be explained by the fact that we carried out a multi centered study.We found a very low utilization of HU at the CHY(2%) as opposed to 43% found at the Frantz Fanon Medical Foundation. The difference between these two values can be explained by the fact that sicklers at the Frantz Fanon Medical Foundation have been using HU since 10 years meanwhile at the CHY,the introduction of HU in management of sicklers is of recent. The value got from the CHY is different from the 13% obtained by Seungue et al. [18] at the Chantal Biya Foundation (CBF) of yaounde in 2014.This can be explained by the fact that the introduction of HU is recent at the CHY and sensitization of patients is ongoing contrary to the Frantz Fanon Medical Center where it is effective since 10 years. Ademola S et al. in March 2017 [19] got a very low percentage use of HU in sicklers in Nigeria. This similarity can be explained by the fact that Nigeria and Cameroon are developing countries where the inhabitants have low income meanwhile treatment with HU is relatively expensive since all these studies were carried out in public hospitals.

The median age of our participants was 22 years with extremes of 4 and 50 years; this is different from the mean age of the population of Hafiz et al. in Yemen [20] that stood at 12 years with the extremes from 5 to 30 years; quite similar to that of Singh et al. in India [17] where it was 20 years. These differences can be explained by the fact that Yemen has a younger population than Cameroon and India. In Cameroon, the median age of the population is 19.4 years. We found a sex ratio of 1.2 in favor of the female sex; contrary to the 1.3 ratio in favor of males that Hassanatou found. In our context, this finding is probably because of the higher proportion of the female sex in the general population.

Our patients were treated for a mean period of 35 months with extremes from 3 to 168 months. Hafiz et al. in Yemen [20] found patients who were treated for a mean period of 18 months; with extremes of 3 to 48 months. Ademola et al. in Nigeria in 2017[19] had in their series patients who were treated for a mean period of 26 months with extremes from 1 to 120 months. Our patients were receiving an average dose of 20mg/Kg/day just like in the study by Mellouli et al. in Tunisia [16] ,or Hassanatou et al. in Cameroun [15] that stood at 15 to 20mg/Kg/day or even of singh et al. in India that was at 22 mg/Kg/day [17]. This similarities can be explained by the fact that the mean dosage that induces clinical benefits is 20 mg/kg/day [21]. The principal indication of HU in our study was the presence of more than 3 VOC per year with hospitalization, followed by increased level of blood transfusions. These results are similar to those of Hassanatou [15] et al. in Cameroon or of Mellouli et al. in Tunisia [16], and of Ademola et al. in Nigeria [19] and in many other studies [10, 11,12,14,22]. This similarity can be explained by the fact that VOC represents the most frequent manifestation of sickle cell disease. In our study the number of VOC passed from 10.83 to 3.5 per year in the patients. This decrease is similar to the series of Singh et al. in which the mean number of crises went from 3.63 to 1.67 at the end of one year of treatment [17]. Similarly a significant reduction of the number of crises was observed in Gilmore et al. in London [23], in Hassanatou et al*.* [15] where the number of VOC went from 12 to 3 by the end of one year. This is because HU enhances the percentage of HbF and it also increases the level of nitric oxide

(NO). The increased HbF reduces the polymerization of HbS and the NO produced, being a powerful vasodilator decreases the frequency of VOC. Our mean number of hospitalization went from 3.33 to 0.88 per year. This is similar to the result obtained by Singh et al. in 2017 [17], where the mean number of hospitalizations went from 4,75 to 2,25 per year. The duration of hospitalization went from 6,97 to 4,80 per year. Hassanatou et al. [15] found a decrease in the number of days of hospitalizations from 9 to 2 days in the space of one year. The mean number of blood transfusions passed from 1,38 to 0,33 per year. Hassanatou et al. [15] found a decreased mean from 2.56 to 1 by the end of one year; similarly Mellouli et al. in 2013 [16] found that their figure went from 1,6 transfusions/patient/year to 0,15 transfusion/patient/year.

We observed a good clinical response in our patients; marked by a reduction in VOC, a reduction in number of hospitalizations and a reduction in the number of blood transfusions. We reason that these reductions are due to HU enhancing the level of HbF which in turn reduces HbS polymerization. Another reason is the production of NO by endothelial cells and the modulation of the inflammatory process and having an amelioration of the major sickle cell syndrome. We did not have a statistically significant difference between patients in long term and those treated in short term. This could be explained by the high percentage of non-compliance. In fact the more the treatment duration increases the more it becomes difficult to support especially in the financial aspect not forgetting discouragements that could occur due to the fact of taking treatment for a long period of time.

The level of mean HbF in our study went from 8.19 to 15.54% per year thus a variation of 7.35%. Singh et al. [17] found a variation of 6,34% (from 12,83 to 19,17), Hassanatou [15] found 9% (from 12% to 21%), the *Multicenter Study Of Hydroxyurea* in United States found 6% [9], Hafiz et al. [20] got 4,7% (from 10 to 14,7%), Mellouli et al. [16] had 27% (from 3 to 30%). These differences can be explained by the difference in duration of treatment or by the genetic variability of populations because we worked in populations with particular differences and the response to the administration of HU varied with respect to genetic variations [24]. Elsewhere the variations we got in our study was equal to those of other studies except that of Mellouli [16]. This is explained by the fact that the response to HU is independent on age [25] because Hassanatou et al worked in a pediatric population and we carried out our study in a mixed population; having children and adults. Singh et al. [17], the *Multienter Study of hydroxyurea*, and Hafiz et al. all had similar populations [20].

We had an increase in Hb level from the base with a mean that went from 7,38 to 8,57 g/dL, with variation of 1,19 g/dL. This variation is comparable to that of Ike Oluwa et al. in Nigeria in 2015 (1,18 g/dL) [18] or that of Strouse et al. in the United States in 2008 (1 g/dl) [26]. It is inferior to that of Hafiz et al. [20] (variation of 1,9 g/dL), of Mellouli et al. [16] (1,8 g/dL) but superior to that of Singh et al. [17] (variation of 0,83 g/dL).

These differences can be explained by the fact that several factors besides HU influence the level of Hb for example nutrition, infections by *Plasmodium falciparum* and the presence or absence of comorbid factors. A significant decrease in the level of leucocytes and platelets was observed like in other studies with means that went respectively from 14037 to 10945 and from 453570 to 364966. This decrease can be explained by the fact that HU provokes a decrease in leucocytes via inhibition of ribonucleotide reductase and by medullary cytotoxicity [27] and a decrease in the activation of platelets by induction of NO synthesis [28]. HU provokes macrocyosis and this was verified in our study. Infact the mean Mean Corpuscular Volume(MCV) went from 88,63 to 94fL, thus a variation of 5,37fL, comparable to the variation of 7,5fL obtained by Hassanatou [15] et al. or of 7,3fL obtained by Singh et al. [17].

Our patients had good compliance at 60% level, close to the level of observance of Hassanatou [15] that was 57,5%. Nonetheless this value is inferior to that of Mellouli et al. [16] who got a level of compliance of 96.94% but superior to that of Ademola et al. [19] in Nigeria (20%).The most frequent cause of bad compliance was the lack of financial resources. Similar in the series of Ademola et al. in Nigeria. [19]. In reality the box of treatment costs 5600 F CFA, made of 24 capsules. Patients have to take on average 2 per month thus 11200 F everymonth; this is not affordable by all patients since 50% of these patients had monthly revenues less than 100.000 FCFA. Tunisia is a developed country and has enough financial resources to take care of health issues of its population contrary to Nigeria and

Cameroon which are both developing countries and patients have to provide for their medical bills. No patient had a lack of medication as found in the series of Hassanatou et al. in Cameroon [15] in 2014 where 57% of patients' lacked medications. This illustrates the efforts that have been made by the Ministry of Public Health and pharmacies to make availablel HU.

65% of patients had no side effects, compared to the series of Ademola et al. in Nigeria [19], where 83,3% did not have any side effect. This can be explained by the absence of usage of high doses. Infact we did not have in our series patients with dosage above 25 mg/kg/day since the toxicity of HU is high above 35 mg/kg/day [21].

5. CONCLUSION

This study has demonstrated the efficacy of HU therapy in reducing Sickle cell diseases complications with few side effects; we thus recommend its use in Sickle cell disease patients in African countries. We also found:

A good clinical response marked by statistically significant decrease of 68% in the number of VOC per year;

A good biologic response marked by a statistically significant increase of 7.35% on level of HbF.

Many patients (40%) had a bad compliance to treatment

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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