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Use of Hydroxyurea in Severe Forms of Sickle Cell Disease: Study of 60 Pediatric Cases in Senegal

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Abstract

Introduction: Sickle cell disease is a serious illness due to its complications (stroke, acute chest syndrome, vaso-occlusive crises [VOC], etc.). Therapeutic strategies have therefore been developed. These include curative therapies as well as palliative therapies, among which hydroxyurea holds a key role in the management of severe forms of sickle cell disease in children. Our study focused on evaluating the use of hydroxyurea at the Outpatient Care Unit for Children and Adolescents with Sickle Cell Disease (USAD) of the Albert Royer National Children's Hospital Center (CHNEAR) in Dakar. **Methodology:** This was a prospective, longitudinal, and descriptive study on a cohort of patients monitored for major sickle cell syndrome (MSS) over one (1) year (May 2023-April 2024), enrolling 60 patients. We included all patients followed for MSS who were receiving hydroxyurea treatment and had up-to-date medical records. **Results:** The patients had an average age of 12 years, with an equal distribution between boys and girls. Complications of sickle cell disease were recorded in 70% of patients, with a high prevalence of stroke (64.29%). Hydroxyurea led to a slight increase in hemoglobin levels after one year of treatment (median of 8.43 g/dl compared to 7.81 g/dl at baseline). Biological parameters such as ASAT and ALAT also showed a downward trend over the course of treatment. Acceptance of hydroxyurea treatment was unanimous among parents, with 80% judging the impact of the treatment as positive, particularly in terms of reduced pain and hospitalizations. **Conclusion:** Our study demonstrates the effectiveness of hydroxyurea in reducing vaso-occlusive crises and hospitalizations in sickle cell patients, thereby improving their quality

of life.

Keywords

Sickle Cell Disease, Hydroxyurea, Child

1. Introduction

Sickle cell disease is an inherited hemoglobin disease due to a mutation in the hemoglobin beta gene, resulting in normal hemoglobin A being replaced by abnormal hemoglobin S [1]. In Black Africa, sickle-cell anaemia is the most common haemoglobinopathy and still affects 10 to 40% of the population in some regions of sub-Saharan Africa [2] [3]. In Senegal, the prevalence of hemoglobin S is estimated at 10%, of which 1% is represented by homozygous forms [4]. Drepanocytosis is a serious disease due to its complications (stroke, acute chest syndromes (ACS), vaso-oclusive crises (VCO), etc.).

To reduce these risks of complications, therapeutic strategies have been developed. These are curative therapies such as hematopoietic stem cell transplantation (HSC), and gene therapy; but also palliative therapies such as transfusion therapies, immunotherapy and hydroxyurea. Among all these strategies, hydroxyurea then appears as a therapeutic alternative for certain patients [5] [6]. It is an antimetabolite that has been shown to be effective in some severe forms of sickle cell disease [5] [6]. Hydroxyurea mainly acts on the bone marrow by stimulating the production of fetal Hb which is a powerful inhibitor of polymerization [5] [6]. In our conditions of practice, its prescription was often limited by its low availability in pharmacies, the reluctance of parents and the lack of trained human resources for its use. The opening of an Outpatient Care Unit for Children and Adolescents with Sickle Cell Disease (USAD) in 2017, the training of human resources on sickle cell anemia as well as the action of volunteer donors, have contributed to facilitate the prescription of this molecule, when the indication was presented.

We report our experience in the use of hydroxyurea, in children with homozygous sickle cell disease (SCD) and followed in a specialized hospital.

2. Materials and Methods

It was a prospective, longitudinal and descriptive study on a cohort of patients with major sickle cell syndroms during one (1) year (May 2023-April 2024) enrolling 60 patients. This work took place at the Outpatient Care Unit for Sickle Cell Children and Adolescents (USAD), of the Albert Royer National Children's Hospital Center (CHNEAR) in Dakar, Senegal. We included all patients during our study period, under treatment with hydroxyurea, with up-to-date medical records.

Before the start of hydroxyurea, all patients had a kidney test, a liver test to eliminate children with severe impairment in the function of these two organs.

Informed parental consent was required. Were excluded from this study, children whose age was less than 2 years, those whose parents had not given their consent, renal and hepatic insufficiencies as well as those whose follow-up was irregular. The initial dose of hydroxyurea was 10 to 15 mg/kg/day, administered in the form of capsules of 500 mg of Hydrea, distributed over 3 to 7 days per week depending on the child's weight. The dose gradually increased in case of clinical ineffectiveness, at a rate of 5 mg/kg/day every 3 months, without exceeding 30 to 35 mg/kg/day and without signs of myelotoxicity or side effects. The follow-up was ensured at (M1, M3, M6, M12) by a clinical examination to assess the degree of effectiveness of the drug and its degree of tolerance, a biological assessment including a blood test, a renal and hepatic evaluation. The basal hemoglobin level was calculated based on the average over the year preceding the start of hydroxyurea administration, excluding any episode of acute complications (infection, acute anemia). Medication adherence was calculated by expressing the ratio of the number of days of effective hydroxyurea intake to the total number of prescribed days. All our patients were supplemented daily with folic acid and children under 5 years of age received oral penicillin.

Severe forms of SCD: SCD with/or (kidney damage; priapism; stroke; acute chest syndrom; acute osteonecrosis of femoral head; more than 3 VCO per year; more than 3 hospitaliszations per year; baseline hemoglobin level below 7 g/dl).

3. Results

Our study involved 60 patients over a period of 12 months.

3.1. Civil Status

3.1.1. Age

The average age of patients was 146.23 months (12 years) ± 55.60 (4.5 years). The median was 144 months, with extremes ranging from 48 months (4 years) to 264 months (22 years) (Figure 1).

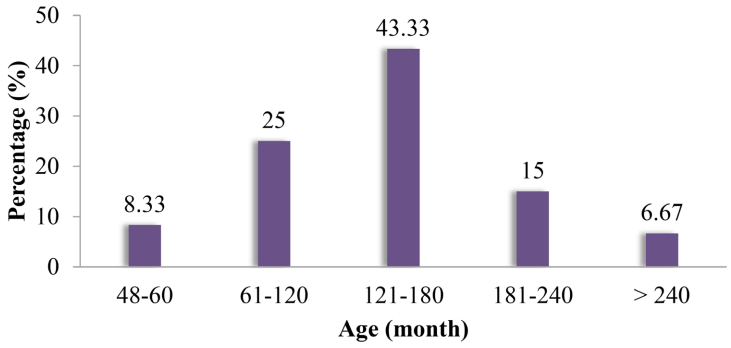

Figure 1. Age of patients.

3.1.2. Sex

There were as many boys as girls, the sex ratio was 1.

3.2. Characteristics of Drepanocytosis

3.2.1 Basic Haemoglobin Levels before Starting Hydroxyurea

The median of basal haemoglobin before starting hydroxyurea was 8 g/dl, with extremes ranging from 6.5 to 9 g/dl (Figure 2).

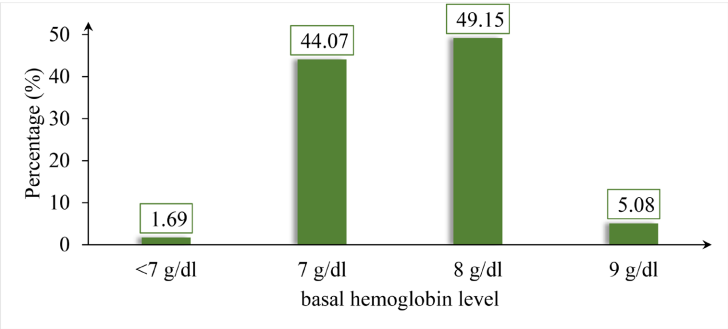

Figure 2. Median of the basal hemoglobin level before starting hydroxyurea.

3.2.2. Complications

Complications of sickle cell disease were observed in 42 patients, or 70% of the study population.

3.2.3. Types of Complications

The different types of complications observed in patients are shown in Table 1. Cerebrovascular accidents (strokes) were observed in 64.29% of patients.

Table 1. Complications of sickle cell disease observed in patients.

Types of complications	Frequency	Percentage (%)
Stroke	27	64.29
Aseptic osteonecrosis of the femoral head	9	21.43
ACS	6	14.29
Priapism	4	9.52
Total	42	100.00

3.3. Hydroxyurea

3.3.1. Start-Up Year

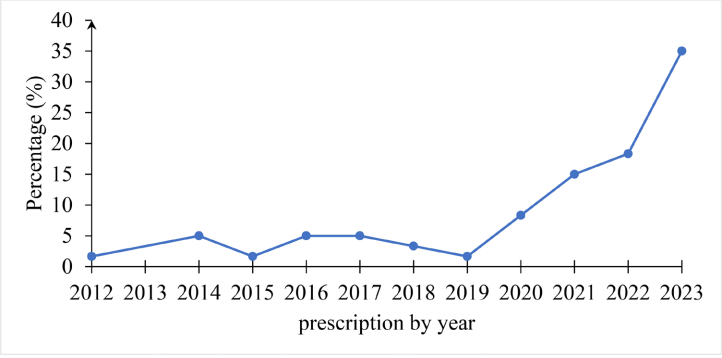

Figure 3. Hydroxyurea prescription by year.

The oldest hydroxyurea prescription in our patients dates from 2012 with a peak of prescription between 2022 and 2023 (Figure 3).

3.3.2. Age at Start of Hydroxyurea

The mean age at start of hydroxyurea was 116.88 months (9.7years) ± 49.90 (4 years). The median age was 120 months (10 years) with extremes ranging from 36 months (3 years) to 228 months (19 years).

3.3.3. Indications of Hydroxyurea

Hydroxyurea was prescribed in 45% of patients for a stroke-related complication. The two other most common indications were the symptomatic character of sickle cell disease (Figure 4).

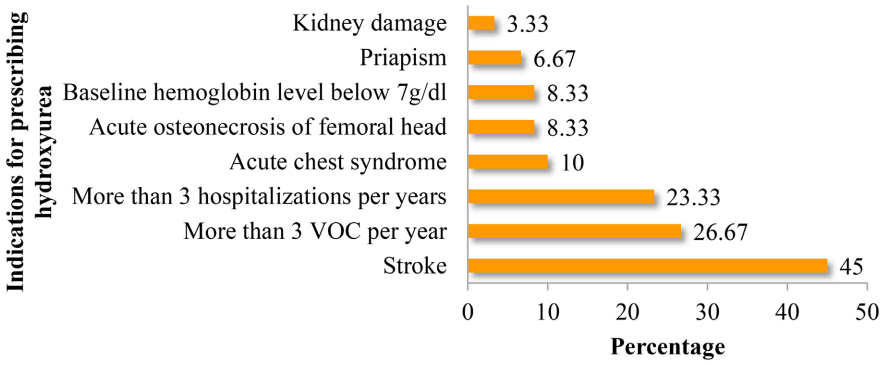

Figure 4. Prescribing indications for hydroxyurea.

3.3.4. Initial Reactions of Parents

The initial reaction of the parents was acceptance for all patients in the study.

3.3.5. Impact of Taking the Water According to the Parents

The impact of taking hydroxyurea was considered positive by 80% of parents (Figure 5).

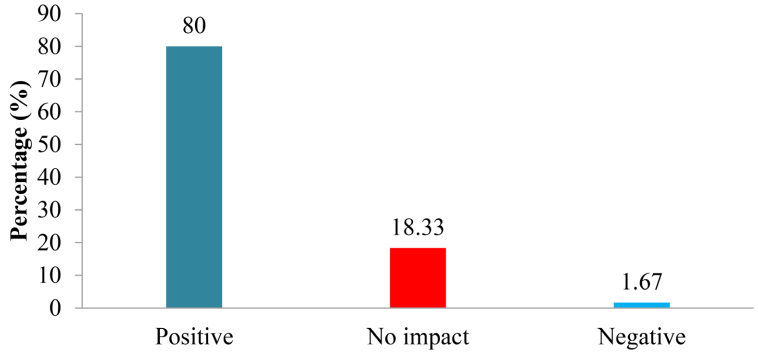

Figure 5. Impact of hydroxyurea according to patients' parents.

3.3.6. Positive Effects Observed under Hydréa by Parents

The positive effects were mainly related to the reduction of pain and the frequency of hospitalizations for pain (Figure 6).

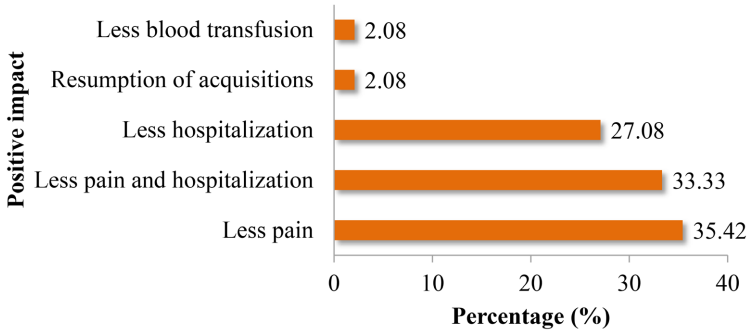

Figure 6. Positive effects of hydroxyurea reported in patients.

3.3.7. Biological Characteristics under Hydroxyurea

1) Haemogram

Blood count monitoring showed a slight increase in haemoglobin compared to baseline (**Table 2**).

Table 2. Average change in blood test parameters under hydroxyurea.

Period	Haemoglobin (g/dl)	White blood cells (10^3/mm^3)	Red blood cells (10^6/mm^3)	Platelets (10^3/mm^3)
D0	7.81	13.82	2.72	410.33
J15	7.98	12.81	2.69	465.55
M1	7.94	12.15	2.69	408.51
M3	7.94	11.78	2.73	391.68
M6	8.15	11.19	2.86	389
1 an	8.43	12.57	2.9	406.64

2) Evolution of other biological parameters

The evolution of other biological parameters is illustrated in **Table 3**.

Table 3. Evolution of other biological parameters.

Period	Reticulocyte count (%)	Transaminases (ASAT) (UI/l)	Transamianses (ALAT) (UI/l)	Uricemia (g/l)	Serum creatinine (Mg/l)
D0	9.76	46.12	29.34	0.16	4.92
M1	9.1	43.43	28.81	0.14	4.94
M3	9.1	33.76	25.9	0.14	5.24
M6	9.28	27.7	21.34	0.13	5.39
1 an	9.89	24.46	16.95	0.12	4.74

ASAT: 0 - 42 UI/l; ALAT: 0 - 41UI/l; Uricemia: 0.10 - 0.45 g/l; Serum creatinine: 4 - 13 mg/l.

3.3.8. Negative Effects Observed with Hydroxyurea Elongated Parents

The negative impact was the occurrence of a stroke recurrence in one patient from the study.

3.3.9. Difficulties Reported

A number of difficulties were reported in some patients or their parents (n = 14).

These difficulties were related to the high cost and unavailability of the drug (Figure 7).

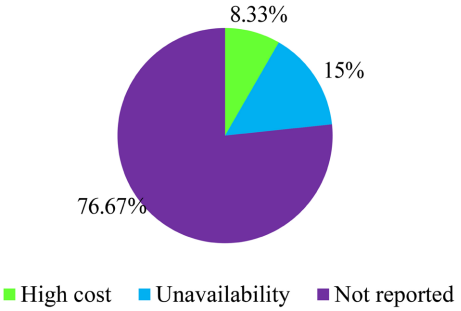

Figure 7. Difficulties reported by patients and their parents.

4. Discussion

In our study, 43.33% of children with sickle cell disease on hydroxyurea belonged to the age group 121 to 180 months. This percentage is higher than that reported by Diop *et al.*, where 65.72% of patients were older than 180 months [7]. In contrast, in the study by Mabiala-Babela *et al.* at CHU Brazzaville, a significant proportion of children under 5 years old were hospitalized for severe complications, with 34.3% of vaso-oclusive crises occurring in these young children [8]. Sex was evenly distributed in our cohort, with 50% boys and 50% girls. This distribution is slightly lower than that observed by Diop *et al.*, who reported a male predominance of 54.28% [7]. Similarly, Boiro *et al.* found a sex ratio of 1.42 [9]. Dème/Ly reported no gender predominance in his study [10]. This balanced distribution in our study population could be due to the autosomal recessive mode of transmission of sickle cell disease.

The mean basal haemoglobin level in our study was 7.5 g/dl, similar to that reported by Diop *et al.*, who found a mean of 7.3 g/dl [7]. However, in the study by Thiam, the average hemoglobin level was slightly higher than that of our patients (8.6 g/dl) [10] [11]. This situation could be partly explained by the study framework of Thiam *et al.* which is a natural region with many natural resources (greenery, sea, natural foods). The mean age at start of hydroxyurea treatment in our study was 10 years. An age lower than that observed by Diop *et al.*, who found a mean start-up age of 15 years [7]. On the other hand, Montalembert reported an average starting age comparable to ours, around 9 years [12]. The main indication for the initiation of hydroxyurea in our study was vaso-oclusive crises (VCO), representing 70% of cases, followed by acute chest syndrome (ACS) and severe anemia. These figures are comparable to those reported by Diop *et al.*, who reported VCO as the primary indication in 71.43% of cases, followed by ACS (25.71%) and severe anemia (34.28%) [7]. In the Montalembert study, VCO also represented the majority of indications, although the percentage is slightly lower (65%) [12]. In contrast, a more recent study by Tshilolo *et al.* had reported a

higher proportion of patients treated for ACS (30%), indicating particular attention to this complication in certain regions [13]. After the initiation of hydroxyurea treatment, we observed a significant reduction in pain and length of hospitalization. The mean duration of sickle cell crises in our study was significantly shorter after initiation of hydroxyurea, with a notable reduction in days of hospitalization. Our results are comparable to those observed by De Montalembert, who found that the duration of hospitalizations was significantly reduced in patients on hydroxyurea [12]. Similarly, Diop *et al.* had reported that the majority of patients on hydroxyurea had hospitalizations of less than 7 days, as was the case with our patients. The positive impact of the treatment was evident, with 80% of patients reporting a significant improvement in their quality of life, reduced pain and hospitalizations, as well as improved haematological parameters. These results were similar to those reported by Diop *et al.*, who had observed a reduction in the number of seizures to 1 or 2 per year in 62.86% of patients [7]. Montalembert had observed a comparable reduction, with a decrease in seizures to less than 2 per year in 70% of patients [12]. Mellouli *et al.* in Tunisia had shown even more favorable results, with 55.26% of patients no longer experiencing iterative VCO or recurrent ACS [14]. A recurrence of stroke was observed in one patient, representing 1.67% of cases. This recurrence could be due to poor adherence to treatment or a lack of expected therapeutic response. However, several cases of stroke, sometimes fatal, are reported in the literature in children with sickle cell anemia treated with hydroxyurea [15]-[17]. Which suggests the existence of genetic or epigenetic factors for tolerance or resistance to hydroxyurea that should be explored in other studies with more patients. Regarding the tolerance of hydroxyurea during our study, we did not find any liver damage nor any kidney damage. There was also no myelotoxicity. An important point to highlight is the lack of control of hemoglobin electrophoresis after hydroxyurea administration. Thus, it is difficult to evaluate the direct effect of hydroxyurea on the different hemoglobin fractions of our patients. In reality, the absence of these data could be attributed to several factors. First of all, the financial constraints but also the unavailability of this analysis in certain health structures. In common practice, in our practice contexts, it is the clinical follow-up that is privileged, for the evaluation of the effectiveness of this treatment, on the symptoms of the disease. The monitoring of hematological parameters being more easily done with blood tests. This lack of post-processing data constitutes a significant limitation of our study. Our study strengthened the evidence for the positive effects of hydroxyurea use in children with sickle cell disease. However, further research is needed to better understand the differences in therapeutic response and tolerance from one patient to another but also the mechanism underlying residual complications. This will allow to refine the indications and adapt the dosages for this vulnerable population.

5. Conclusion

Our study highlights the effectiveness of hydroxyurea and its positive impact in the management of sickle cell patients. The initiation of treatment has signifi-

cantly reduced the frequency and duration of vaso-oclusive crises, as well as hospitalizations, thus contributing to a significant improvement in the quality of life of patients. However, despite these promising results, challenges persist, particularly regarding understanding and adherence to treatment, as evidenced by the case of stroke recurrence observed in our cohort.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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