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Factors Influencing Adherence to Hydroxyurea Treatment Among Children with Sickle Cell Disease at the Mother and Child Center of the Chantal Biya Foundation

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Summary

Introduction: Sickle cell disease (SCD) is a genetic hemoglobin disease for which there are many treatment options. Evidence supports the efficacy and cost-effectiveness of hydroxyurea (HU). Nevertheless, its use and adherence to treatment remain suboptimal, hence, the necessity to assess the factors influencing this observance.

Objectives: The objective was to evaluate the factors influencing observance to HU in children with sickle cell disease from the Mother and Child Center of the Chantal Biya Foundation (MCC of the CBF).

Materials and Methods: This was a descriptive and analytical cross-sectional study from January to June 2020. Children on HU for at least six months, and followed up at MCC of the CBF were included. Data collection was done using a pre-tested questionnaire. The level of compliance was assessed using the Morisky's observance grid, where 8 points was considered as "good"; 6-7 points as "fair", and <6 as "poor". Data were stored in CSPro version 7.0 software, and subsequently analyzed using the SPSS version 20.0 software.

Results: Of 142 patients recruited, the level of patient observance was considered "good" in 2.1%, fair in 26.1% and poor in 71.8%. Logistic regression analyses suggested that using hydroxyurea to prevent complications was the only factor that favored good medical adherence [OR=0.37; CI (0.14-0.987)] (p=0.047). Poor compliance was mainly associated with the fear of infertility and and other sides effects associated with the use of HU.

Conclusion: Children with SCD in this study have poor compliance with HU. Implementing IEC sessions would make it possible to raise patient/parent awareness and reverse this trend.
Keywords: Sickle Cell Disease, Hydroxyurea, Observance

List of Abbreviation:

SCD: Sickle Cell Disease

YUTH: Yaounde University Teaching Hospital

MCC: Mother and Child Center of the Chantal Biya Foundation

HU: Hydroxyurea

Introduction

Although sickle cell disease is found worldwide, it is mainly present in black people from sub-Saharan Africa [1]. In Cameroon, the prevalence of the sickle cell trait is 21.6% [2]. With improved health care, the infant survival rate has risen to almost 50% in Africa [3]. In Africa, only 10% of SS sickle cell patients reach adulthood, but this percentage seems to be improving in recent years [4].

Patients with sickle cell disease experience several lifelong complications [5]. Compared to healthy controls, patients with sickle cell disease experience a significant decline in health-related quality of life (HRQOL) due to disease-related complications [6]. For the past two decades, HU, chronic transfusions, and stem cell transplantation have been treatment options for patients with sickle cell disease [7]. HU is a myelosuppressive agent first used in sickle cell disease in 1984 with the central role of producing fetal hemoglobin. In addition, it is involved in increasing the hemoglobin level, reducing the level of white blood cells, reducing the incidence of vaso-occlusive crises, and delaying the occurrence of complications related to sickle cell disease [5]. Barriers to adherence to HU include forgetfulness, fear of side effects (e.g., congenital disabilities and risk of cancer), limited knowledge about HU, and misperceptions of the severity of HU in sickle cell disease [8-9].

Numerous studies supported the efficacy and cost-effectiveness of using HU in adult and pediatric patients with sickle cell disease with benefits in reducing morbidity, mortality, and improved HRQoL [10-12]. Nevertheless, the use of HU and adherence to treatment remain suboptimal in this population [13-15]. In Africa, a study carried out in Nigeria in 2017 revealed a lack of observance linked to a low level of knowledge, misuse, and unavailability of drugs [9]. Having an idea of the quality of therapeutic adherence would be very useful in improving patient care and, in turn, quality of life.

Therefore, it seemed rational to conduct this study whose general objective was to aimed at assessing factors associated with observance of HU in children with sickle cell disease at the Mother and Child Center of the Chantal Biya Foundation (MCC of the CBF). More specifically, it involved determining the proportion of patients on HU, describing their socio-demographic characteristics, assessing their therapeutic compliance with HU using a standardized evaluation, and identifying the factors influencing this therapeutic observance of HU.

Methodology

Following acquisition of a research authorization and ethical clearance a descriptive and analytical cross-sectional study was conducted from January to June 2020 at the Mother and Child Center of the Chantal Biya Foundation, which is a level 1 referral pediatric hospital located in Yaoundé, Cameroon.

Our population consisted of all children with sickle cell disease aged 0-18 years on HU for at least six months, and followed up in this health facility. We carried out consecutive sampling. All children for whom we did not obtain informed parental consent and adolescent assent were excluded from the study.

Data were collected from participants using a pre-established and pre-tested questionnaire. This questionnaire included several sections: socio-demographic characteristics (age, sex, place of residence, religion, educational level of the child and profession of the person in charge). Observance, was studied using the Morisky observance grid (MMAS -8) [16]. It has 8 questions on whether or not to forget to take medication depending on the circumstances, the factors influencing therapeutic observance. Regarding observance, 8 questions were asked, rated from 0 to 1 each for 8 points. This gave three levels of compliance: good observance (8 points), average observance (6 and 7 points), poor observance (<6 points). Questionnaires that were not exploitable (incomplete…) were excluded from the study.

Data analysis was done using Census and survey processing (CSPro) 7.0 software and SPSS software (Statistical Package for the Social Sciences) version 20.0.l. For the search for associated factors, we used the Chi² and Fisher test. The multivariate analysis was done by logistic regression. The degree of association was measured by the Odd Ratio and its 95% confidence interval. A p-value less than 0.05 was considered statistically significant for a 95% confidence interval.

Results

Poor observance was found in 71.8% of children on hydroxyurea. (Figure I) During the study period, 313 children with sickle cell disease were received at the Mother and Child Center of the Chantal Biya Foundation, including 186 children on HU, which accounts for 59.4%. Among the 186 children on HU, 17 refused to participate in the study and 27 had incomplete questionnaires. Our sample was therefore 142 children on HU. The male sex was the most represented (74, 52.1%) with a sex ratio of 1.08. The average age of the patients was 10.25±4.18 years (range 01 – 18 years and the most frequent age group was that of [6-12 years] with 47.2%. Table I shows the socio-demographic characteristics of our study sample.

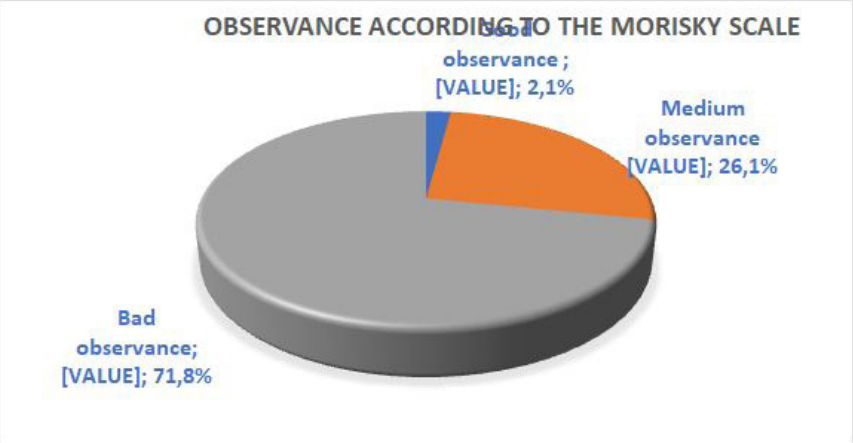

Figure 1: Assessment of observance according to the Morisky scale scoring grid in 142 children with sickle cell disease under hydroxyurea in Yaoundé in 2020

Variables	Number(n=142)	Pourcentages (%)
Sex		
Male	74	52.1
Female	68	
Age (in years)		
[0-6]	19	13.4
[6-12]	67	47.2
[12-18]	56	39.4
Respondent's education level		
Unschooled	6	4.2
Primary	60	42.3

Variables	Number(n=142)	Pourcentages (%)
Secondary	63	44.4
Superior	13	9.2
Place of residence		
Rural	23	16.2
Urban	119	83.8
Guarantor's profession		
Unemployed	9	6.3
Trader	37	26.1
Private sector	39	27.5
Public sector	54	38
Others	3	2.1
Religion Christian Muslim	124 18	87.3 12.7

Table 1: Sociodemographic characteristics of 142 children with sickle cell disease on hydroxyurea in Yaoundé in 2020

No association was found between observance and gender, age, level of education, or place of residence. Having a merchant as a guarantor was significantly associated with poor observance with an estimated risk of 4 times [OR=4.30; CI (1.41-13.1)] (p=0.006). On the other hand, the fact that the guarantor worked in the public sector was a protective factor [OR=0.4, IC (0.2-0.8)] (p=0.009). Patients considering the drug to be effective were five times more likely to have fair to good observance. [OR=0.2; CI (0.45-0.91)] (p=0.023). Knowing that HU could reduce seizures was a protective factor against poor observance [OR=0.16; CI (0.04-0.72)] (p=0.008). Similarly, knowing that this drug could prevent disease complications favored observance [OR=0.4; CI (0.2-0.91)] (p=0.026). Fear of using HU and especially fear of infertility were significantly associated with poor observance with an estimated risk of 2.9 and 4 respectively [OR=2.91; CI(1.22-6 .95)](p=0.013) and [OR=4; CI(1.13-14.11)](p=0.022). Patients keeping doctor appointments were significantly associated with good compliance [OR=0.22; CI (0.09-0.53)] (p=0.000). Table II describes the factors influencing observance in our study population.

Variables	Observance		OR (IC à 95%)	Valeur p
	Bad n (%)	**Good (Medium/ Good) n (%)**		
Socio-demographic factors				
Guarantor's profession				
Unemployed	7(7.0)	2(5.1)	1.4(0.3-7.05)	1.000
Trader	**33(33.0)**	**4(10.3)**	**4.30(1.41-13.1)**	**0.006**
Private sector	28(28.0)	11(28.2)	0.99(0.44-2.3)	0.995
Public sector	**32(32.0)**	**22(56.4)**	**0.4(0.2-0.8)**	**0.009**
Drug-related factors Evaluation of efficacy by the patient				
1=yes (helpful)	**81(79.4)**	**38(95.0)**	**0.2(0.45-0.91)**	**0.023**
2=no (non helpful)	21(20.6)	2(5.0)		
Reasons for effectiveness				
1= seizure reduction	**77(75.5)**	**38(95.0)**	**0.16(0.04-0.72)**	**0.008**
2= reduction of anemia	29(28.4)	15(37.5)	0.7(0.31-1.43)	0.293
3= increases years of life	10(9.8)	4(10.0)	0.98(0.3-3.32)	1.000
4 = prevent complications	**18(17.6)**	**14(35.0)**	**0.4(0.2-0.91)**	**0.026**
5 = reduce hospitalizations	41(40.2)	23(57.5)	0.5(0.24-1.04)	0.062

Variables	Observance		OR (IC à 95%)	Valeur p
	Bad n (%)	**Good (Medium/ Good) n (%)**		
6 = reduction of infections	9(8.8)	4(10.0)	0.87(0.25-3)	
Concerns about the use of HU				
1=yes	**43(42.2)**	**8(20.0)**	**2.91(1.22-6.95)**	**0.013**
2=no	59(57.8)	32(80.0)		
Reason for fear of use				
1 = death	4(3.9)	3(7.5)	0.5(0.11-2.34)	0.402
2 =cancer	10(9.8)	5(12.5)	0.8(0.24-2.4)	0.762
3 =infertility	**25(24.5)**	**3(7.5)**	**4(1.13-14.11)**	**0.022**
4 =malformation	0	0		
5 =other	5(4.9)	1(2.5)	2(0.23-17.8)	1.000
Patient factor Respect of appointments				
1=yes	**48(47.1)**	**32(80.0)**	**0.22(0.09-0.53)**	**0.000**
2=no	54(52.91)	8(20.0)		

Table 2: Factors influencing HU compliance in 142 children with sickle cell disease in Yaoundé in 2020

After logistic regression, knowing that hydroxyurea helps prevent complications was a factor in good medical observance. (Table III)

Variables	Observance		ajusteD OR (IC AT 95%)	ajusteD P VALUE
	Bad	**Good (Medium+good)**		
Trader	33 (89.2)	4 (10.8)	3.34 (0.902-12.4)	0.071
Public sector	32 (59.3)	22 (40.7)	0.47 (0.17-1.27)	0.139
HU efficiency yes(efficient)	81 (68.1)	38 (31.9)	0.64 (0.054-7.5)	0.179
1 = seizure reduction	77 (67)	38 (33)	0.53 (0.05-5.7)	0.598
4=prevent complications	**18 (56.3)**	**14 (43.8)**	**0.37 (0.14-0.987)**	**0.047**
5=reduce hospitalizations	41 (64.1)	23 (35.9)	1.16 (0.45-2.24)	0.762
Fear of Hydroxyurea yes	43 (84.3)	8 (15.7)	2.17 (0.63-7.5)	0.218
Fear of infertility	25 (89.3)	3 (10.7)	2.5 (0.45-2.24)	0.300
Respect of appointments =yes	48 (60)	32 (40)	0.4 (0.15-1.007)	0.052
Rural	19 (82.6)	4 (17.4)		

Table 3: Logistic regression of factors influencing HU compliance of 142 children with sickle cell disease in Yaoundé in 2020

Discussion

This study assessed the level of adherence to HU using the Morisky questionnaire [16], and reports poor compliance with HU in more than two-thirds of the participants (71.8%), which is considerably high, especially when compared to a similar analysis in neighboring Nigeria, in which good observance was reported in 94.4% [17]. The factors associated with good compliance in our study included knowing that HU is effective against SCD, prevents complications and seizures, as well as having a guarantor working in the public sector and the respect of appointments. Nevertheless, it must be noted that in the Nigerian study, the level of compliance was assessed differently. The authors counted the number of remaining tablets/capsules of the drug at each consultation. However, the difference in the outcomes are alarming.

The efficacy of the treatment in terms of reduction in the frequency of seizures was associated with therapeutic observance of HU (p=0.008), which increased the chances of having good therapeutic adherence with HU [OR=0, 16; IC (0.04-0.72)]. Our result is similar to that obtained by Ofakunrin et al. in 2019 in their Nigerian cohort study [RR=0.07; CI (0.02-0.23)] (p=0.001) [17].

The univariate analysis also revealed that the will to prevent complications, the awareness of the effectiveness of HU in reducing the sickle cell crisis and the respect of medical appointments were significantly associated with good therapeutic compliance. This result may be justified by the fact that the patients in our study know and fear the complications of sickle cell disease, which would motivate them to take HU to delay the onset of these complications. This may also indicate the quality of the information, education and communication work and also the quality of the reception provided upstream by the attending physicians on sickle cell disease and the therapeutic modalities. Furthermore, Yawn et al. in 2014 in a study conducted in America [5], revealed that the benefits mentioned by parents of children with sickle cell disease following the use of HU were significantly associated with good compliance with HU (p<0.001).

Being a trader quadruples the risk of poor treatment compliance [OR=4.30; CI (1.41-13.1) (p=0.006). On the other hand, belonging to the public sector is significantly correlated with good compliance with HU [OR=0.4; CI (0.2-0.8)] (p=0.009). This could be due to the fact that commerce in our context does not offer stable and regular financial accessibility to parents for the purchase of HU, unlike work in the public sector.

Moreover, the fear associated with the use of HU, the fear of infertility and all the other side effects were also factors of poor therapeutic compliance. Indeed, fearing the long-term side effects mentioned by patients in our context modifies their perception of HU. Male fertility is likely affected during hydroxyurea treatment by affecting gametes. Sperm storage in a sperm bank has been an option offered to patients in Yaoundé, Cameroon for 8 years. This could, if needed, improve HU compliance, however, the high cost could be a limiting factor in our setting.

After logistic regression, only the fact of taking HU to prevent complications was a factor significantly associated with treatment observance to HU. Indeed, the desire to avoid complications reduced the risk of poor adherence to HU [OR=0.37; CI (0.14-0.987)] (p=0.047).

The study population was 142 patients. This result, higher than that obtained in America in 2017 (34 patients) by Badawy et al. [8], is hardly surprising given that the prevalence of sickle cell disease is higher in Africa than in America. Nevertheless, this result is lower than that found in a multicenter study in 2019 carried out in Angola, Uganda, the Democratic Republic of Congo, and Kenya, which found 600 patients [18]. This can be explained by the fact that the multinational study was carried out in 5 countries, unlike ours, which was carried out in a single health facility and over a shorter period.

We found a prevalence of 59.4% of patients on HU at the FCB CME. In 2017, only 12.7% of children were on HU [19]. The benefits of HU on the quality of life and the reduction of mortality are clear and have probably convinced the nursing staff of its usefulness, hence a sharp increase in the prescription [8]. On the other hand, our result is still lower than that found in Saudi Arabia in 2019, which had evaluated the prevalence of children on HU at 77.6% [20]. This difference could be linked to a difference in the economic power of families between the two countries in the absence of universal medical coverage.

The average age in this study was 10.25 ± 4.18 years; a figure very close to that obtained in a survey carried out in Nigeria in 2019 by Ofakunrin et al. who had found an average age of 8.47 ± 3.89 years [17].

The sex ratio favored the male sex in our study with a proportion of 52.1% of boys. Our result is close to that found in a study in Nigeria in 2019, which was 55.6% [17], although the transmission of Hemoglobin S is not genetically linked to sex.

The secondary level was the most represented with 44.4% because this work involved children under the age of 18 with a large study population in the age intervals 12-18 years, corresponding to the age of secondary school in our context. On the other hand, in a study carried out in Cameroon in 2017, we found 47.1% [19] of children because the most represented age group was that of 5-10 years corresponding to the age of primary level in our context.

Conclusion

At the end of our study, we note an increase in the number of children on HU compared to previous years. However, the vast majority of patients had poor observance with HU. The factors in favor of good observance include knowing that HU is effective, that it prevents complications and seizures, having a guarantor working in the public sector, as well as knowing and respecting of doctor's appointments.

These findings suggest the need to increase the awareness of patients and caregivers on the use of HU in patients with appropriate indications. Establishing a system of subsidies by the public authorities or Universal Health Coverage would also facilitate adherence. IEC (information, education and communication) sessions with patients with indications for HU and their parents would make it possible to make the drug better known and demystify it.

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