Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Impact of Hydroxyurea on Clinical and Biological Parameters of Sickle Cell Anemia in Children in Abidjan

Keywords: Sickle cell; Hydroxyurea; Côte d'Ivoire.

Published: March 01, 2024 **Received: December 27, 2023** **Accepted: February 12, 2024**

Citation: Yayo-Aye M., Adjambri A.E., Kouakou B., N'guessan-Blao R., Adjé L.M., Kamagaté T., Yapo V., Sawadogo D. Impact of hydroxyurea on clinical and biological parameters of sickle cell anemia in children in Abidjan. Mediterr J Hematol Infect Dis 2024, 16(1): e2024026, DOI: http://dx.doi.org/10.4084/MJHID.2024.026

To the editor.

Sickle cell disease results from a point mutation in the sixth codon of the β-globin gene, leading to the synthesis of mutated hemoglobin known as hemoglobin S (Hb S), which can polymerize under deoxygenated conditions. Hb S is responsible for hemolysis and vaso-occlusive events in individuals with sickle cell disease.[1] It stands as the world's leading genetic disease, posing a significant public health challenge in Africa. Indeed, prevalence rates of Hb S in at least 40 African countries range between 2% and 30%, which explains the high level of mortality and morbidity due to sickle cell disease.[2] Currently, the only curative treatments are bone marrow transplantation and gene therapy, which unfortunately cannot be carried out in Côte d'Ivoire due to the high cost and insufficient technical infrastructure. Formerly used in certain hematologic malignancies, hydroxyurea (HU) remains an effective alternative in the treatment of sickle cell disease.[3] Biological monitoring of HU is necessary to ensure a better quality of life for children with sickle cell disease.

It was a prospective observational study that took place from November 2017 to April 2019. Children of both sexes, aged 5 to 15 years, experiencing at least 3 vaso-occlusive crises (VOC) per year were included in the study after obtaining informed and written consent from their parents. Each patient received a daily dose of 15mg/kg of hydroxyurea for 12 months in the form of 500mg capsules. For each patient, a venous blood sample was taken for hematological and biochemical tests. In our trial involving children with SSFA2 (Hb SS) and SFA2 (Sβ 0 thalassemia) sickle cell disease, subjects received a dose of 15mg/kg/day of hydroxyurea for 12 months due to challenges in handling the maximum tolerated dose in developing countries. In contrast, American authors often use doses ranging from 35 to 40 mg/kg/day.[4] A total of 45 children aged 5 to 10 years were selected. The mean age was 9 years.

The SSFA2 hemoglobin phenotype is predominant in our study **(Table 1)**, in accordance with its historical prevalence among major forms of sickle cell disease.[5] The administration of hydroxyurea led to a modification of clinical and biological parameters. With hydroxyurea, we observed a reduction or absence of vaso-occlusive crises, hospitalizations, and transfusions. After 6 months of hydroxyurea treatment, our study found rates of 84.4%, 100%, and 97.8%, respectively, for the absence of VOC, hospitalizations, and transfusions **(Table 2)**.

These rates of reduction in sickle-cell-related events were statistically significant in our study and consistent

Table 1. Distribution of subjects by sex, age, and hemoglobin phenotype.

	Women	Men	Total
Distribution by age group			
	n	**n**	**n (%)**
Children aged 5 to 10	13	15	28 (62.2)
Children aged 10 to 15	5	12	17 (37.8)
Distribution by hemoglobin phenotype			
	n	**n**	**n (%)**
SFA2	3	7	10 (22.2)
SSFA2	15	20	35 (77.8)
Total	18	27	45 (100)

Table 2. Clinical data of subjects before and after hydroxyurea treatment.

Parameters	M0		M6		M12	
	n	%	n	%	n	%
Number of VOC						
0	0	0	38	84.4	41	91.1
[1-3]	0	0	7	15.6	4	8.9
>3	45	100	0	0	0	0
Number of hospitalizations						
0	17	37.8	45	100	44	97.8
[1-3]	14	31.1	0	0	1	2.2
>3	14	31.1	0	0	0	0
Number of transfusions						
0	25	55.6	44	97.8	45	100
[1-3]	10	22.2	1	2.2	0	0
>3	10	22.2	0	0	0	0

Table 3. Changes in biological parameters during patient follow-up.

Parameters	Mean ± SD			*p-value*
	M0	M6	M12	
Hb S (%)	87.5 ± 4.71	75.7 ± 11.9	78.7 ± 12.8	M_0-M_6:< 0.0001 M_0-M_{12}: <0.0001
Hb F (%)	10.3 ± 4.8	22.3 ± 11.9	19.7 ± 12.7	M_0-M_6: < 0.0001 M_0-M_{12}: <0.0001
Hemoglobin (g/dL)	7.24 ± 0.88	8.73 ± 1.2	8.55 ± 1.2	M_0-M_6: < 0.0001 M_0-M_{12}: < 0.0001
MCV (fL)	80.7 ± 9.75	96.6 ± 11.8	88.4 ± 16	M_0-M_6: < 0.0001 M_0-M_{12}: < 0.0001
MCHC (pg)	27.4 ± 3.04	35.1 ± 5.4	34.2 ± 11	M_0-M_6: < 0.0001 M_0-M_{12}: <0.0001
Leucocytes (10^3 cells/mm^3)	15800 ± 1660	9410 ± 3380	9740 ± 3610	M_0-M_6: <0.0001 M_0-M_{12}: <0.0001
Platelets (10^3 cells/mm^3)	403000 ± 117000	337000 ± 166000	346000 ± 147000	M_0-M_6: 0.004 M_0-M_{12}: 0.086
Creatinine (mg/L)	4.4 ± 0.6	5.4 ± 1.3	6.24 ± 1.2	M_0-M_6: <0.0001 M_0-M_{12}: <0.0001
Urea (g/L)	0.16 ± 0.02	0.16 ± 0.04	0.13 ± 0.05	M_0-M_6: 1 M_0-M_{12}: <0.001
AST (UI/L)	45 ± 16	42 ± 16	23 ± 15	M_0-M_6: 0.747 M_0-M_{12}: <0.0001
ALT (UI/L)	21 ± 11	26 ± 16	25 ± 13	0.104*
Total bilirubin (mg/L)	37 ± 23	27 ± 23	18 ± 15	M_0-M_6: <0.0001 M_0-M_{12}: <0.0001
Conjugated bilirubin (mg/L)	10 ± 9	12 ± 10	10 ± 8	0.591*
LDH (UI/L)	633 ± 268	479 ± 128	435 ± 177	M_0-M_6: <0.0001 M_0-M_{12}: <0.0001

**p-value in Friedman's test not significant. Lactate dehydrogenase: LDH*

with findings from various authors.[6] These clinical improvements were even more pronounced after 12 months of treatment overall. The reduction in the frequency of vaso-occlusive crises and hospitalizations

can have a positive impact on the quality of life of these patients. On a biological level **(Table 3)**, we observed a reduction in white blood cell (WBC) and platelet counts. These reductions were statistically significant at 6 months. It is worth noting that a high WBC count is an unfavorable prognostic factor for patients.[7] The increase of these parameters, hematocrit, mean corpuscular hemoglobin concentration, and hemoglobin level, is beneficial as it reduces the frequency of blood transfusions by raising the threshold at which a transfusion should be considered in these patients.[8] The changes in hemogram parameters in our study are similar to those reported by other authors.[6] In our study, the fetal hemoglobin (Hb F) level doubled from 6 months and remained stable until 12 months of hydroxyurea treatment. This induction of Hb F production has been observed by other authors.[9] This increase in Hb F reduces complications related to this disease. Hydroxyurea induces the production of Hb F and increases the volume of red blood cells, thus reducing the risk of Hb S polymerization.[10] This induction of Hb F leads to a decrease in Hb S. In our series, the mean Hb S level decreased from 87.5% to 75.7% after 6 months of treatment, a result beneficial for the patients. Creary et al.[9] also observed this decrease in Hb S with hydroxyurea.

During this clinical trial, we monitored renal and hepatic functions as well as some biochemical parameters. We did not observe any disruption in these functions. The concentrations of creatinine, urea, alanine aminotransferase, aspartate aminotransferase, bilirubin, and Lactate dehydrogenase did not increase after 6 months and 12 months of treatment. Although hydroxyurea is mainly eliminated by renal excretion, instances of kidney toxicity are exceedingly rare, as is hepatic toxicity.[11] At the beginning of the study (M0), a slight increase in bilirubin was noted, reflecting the sub-icterus commonly seen in sickle cell disease. The trend towards a reduction in bilirubin from M0 to M12 suggests the absence of hemolysis, emphasizing the protective effect of hydroxyurea on red blood cells from pathological lysis.[12] Hydroxyurea treatment is deemed safe for patients and has a positive impact on the quality of life for children with sickle cell disease by reducing the frequency of hospitalizations, vaso-occlusive crises, and transfusions.

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Competing interests: The authors declare no conflict of Interest.

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