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The Effect of Hydroxyurea Treatment on Fetal Haemoglobin Level and Clinical Status of Sudanese Sickle Cell Anaemia Patients

YASIR ABDIN BABIKIR
Department of Haematology, Central Laboratory
Omdurman Military Hospital, Omdurman
Sudan
ELSHAZALI WIDAA ALI
Department of Haematology
Faculty of Medical Laboratory Sciences
Al Neelain University, Khartoum
Sudan

Abstract:

This descriptive cross-sectional study was conducted to determine the effect of Hydroxyurea treatment on HbF level and the severity among Sudanese patients with sickle cell disease through the period of June 2013 up to September 2012, using Capillary Electrophoresis technology. The total number of study group was seventy nine Patients, 39 (49.4%) of them were males and 40 (50.6%) were females; their ages ranged between 0.4 -26 years (mean ± SD: 9.0 ± 6.1). According to ethnicity, 35 (44.3%) of them were Afro- Asiatic, 5(6.3%) were Nilo-Sahara and 39 (49.4%) were Niger-Congo. Twenty two(27.8%) of the patients were taken Hydroxyurea therapy (500mg). The study reveals that Hb-F level is ranged (0.9 – 38.5 % mean 8.4%) 47% with HbF < 6.0% and 6.3% with HbF > 20% , this illustrate that Sudanese patient with SCD have low level of HbF and this level is not enough to influencing the clinical crises of the disease. Our results showed that there is no significant different in HbF level of patients inducted Hydroxyurea and those were not and accordingly there was no clear effect on the clinical crisis. As study also explain that no correlation was found between hudroxyurea administration and disease complications : (Pain crisis, Dactylitis, Leg ulcer, Stroke, Acute

chest syndrome, Spleenectomy, Gallstone) the (P,Values : 0.61, 0.20, 0.37, 0.13, 0.52, 0.05, 0.27 respectively) there was no statistically significant different on their complications

Key words: Sickle cell anaemia, Hydroxyurea., Fetal haemoglobin.

Introduction

Sickle cell anaemia, also known as sickle cell disease (SCD) is a worldwide disorder that occurs when the sickle (S) gene is inherited from both parents (homozygous state, SS). Heterozygous inheritance of the sickle gene (AS) is frequently referred to as sickle cell trait, usually it has no clinical consequences. Individuals with SCD exhibit significant morbidity and mortality. Symptoms include chronic anemia, acute chest syndrome, stroke, splenic and renal dysfunction, pain crises, and susceptibility to bacterial infections. (Stiene-Martin A,1998; Ashley-Koch A, 2000**)**

In Sudan, sickle cell anaemia is the one of the major types of anaemia especially in western Sudan where the sickle cell gene is frequent. Previous study about haemoglobinopathies in Sudan showed that haemoglobin "S" is the most common abnormal haemoglobin in western sudanese ancestry. Sickle beta globin (β^s) gene may have been preferentially introduced through migration of people from West African tribes to Sudan particularly hosa, folani and bargo **(**Abdelrahim O, 2006; Rihab E. Bereier, 2007; Abozer Y.Ederdery, 2008**)**

Patients with SCD in populations who inherit a genetic determinant for high fetal hemoglobin (Hb-F) typically have a very mild clinical disorder. Moreover, Hb-F has been identified as a major prognostic factor for several clinical complications of sickle cell anaemia including pain crisis, acute chest syndrome and early death. (Bailey K, 1992; Castro O, 1994; Platt O, 1994**)**

Pharmacological induction of Hb-F production was proposed as a therapeutic strategy to decrease the severity of SCD. Hydroxyurea is one of the drugs used widely to induce Hb-F synthesis in patients with SCD, it is decreases the frequency of painful crises and episodes of acute chest syndrome and reduces transfusion requirements and hospitalizations in patients with moderate to severe SCD. (Fathallah H, 2006; Steinberg MH, 1997; Charache S, 1996).

The usefulness of hydroxyurea on Hb-F level and on patients clinical status in Sudan is not well studied yet. This study aimed to determine the pattern of haemoglobin in Sudanese sickle cell anaemia patients and to study the effect of Hydroxyurea on Hb-F level and patients' clinical status.

Materials and methods

Study subjects and design

This study is a descriptive cross-sectional study conducted at Omdurman military hospital and refer clinics at Fatharahman Elbasheer centre, Khartoum, Sudan, in the period from June to September 2013.

Sample collection and analysis

After informed consent, venous blood samples were collected in ethylene diamine tetra acetic acid (EDTA) blood tubes from 79 sickle cell anaemia patients and analyzed by modified fully automated capillary2 flexpiercing haemoglobin electrophoresis technique to detect and estimate the different types of haemoglobins found in those patients.

Data collection and analysis

Data was collected by structured interview questionnaire and from patients' medical files and analyzed using statistical package for social science (SPSS).

Results:

A total of 79 patients with sickle cell anaemia were enrolled in this study; 39 (49.4%) of them were males and 40 (50.6%) were females; their ages ranged between 0.4 -26 years (Mean ± SD: 9.0 ± 6.1).

According to ethnicity, 35 (44.3%) of patients were Afro-Asiatic, 5(6.3%) were Nilo-Sahara and 39 (49.4%) were Niger-Congo.

Twenty two (27.8%) of the patients were treated with hydroxyurea (500mg), while 57(72.2%) were not.

Mean Hb-F level in study subjects was found to be 8.4% . No statistically significant difference was found in mean Hb-F level according to gender (Mean: 8.1% for males and 8,6% for females, *P,value*: 0.72).

Patients from Niger-Congo group were found to have higher Hb-F level than the other 2 ethnic groups, followed by Nio-Sahara group and Afro-Asiatic group consequently but the difference was not statistically significant (Means: 9,1%, 7,9%, and 7.6% respectively, *P,value:* 0.63).

No statistically significant difference was found in mean Hb-F level in patients using hydroxyl urea and those not using hydroxyl urea (Means: 7.6% and 8.7% respectively, *P,value*: 0.57).

As shown in table (1) there was no statistically significant difference in mean Hb-F level in patients with and without different disease complications.

No correlation was found between hudroxyurea administration and disease complications (Table 2)

Table 1: comparison of Hb-F level in patients with and without complications

Complication		N	Hb-F level		*P.value*
			Mean	SD	
Pain crisis	Yes	36	9.3	7.6	0.499
	No	43	7.57	6.1	
Dactylitis	Yes	4	17.4	9.3	0.35
	No	75	7.9	6.4	
Leg ulcer	Yes	2	11.2	12.7	0.21
	No	77	8.3	6.7	
Gallstone	Yes	3	5.2	1.96	0.187
	No	76	8.5	6.91	
Stroke	Yes	3	4.9	2.3	0.199
	No	76	8.5	6.91	
Acute chest syndrome	Yes	8	7.4	4.9	0.337
	No	71	8.5	7	
Splenectomy	Yes	17	7.7	4.9	0.223
	No	62	8.5	7.2	

Table 2: complications between hydroxyurea administration and disease complications:

Complication		Hyroxyurea		P.value
		Yes	No	
Pain crisis	Yes	9 (41%)	27 (47%)	0.61
	No	13 (59%)	30 (53%)	
Dactylitis	Yes	0 (0%)	4 (7%)	0.2
	No	22 (100%)	53 (93%)	
Leg ulcer	Yes	0 (0%)	2 (9%)	0.37
	No	22 (100%)	55 (96%)	
Stroke	Yes	2 (9%)	1 (5%)	0.13
	No	20 (91%)	56 (98%)	
Acute chest syndrome	Yes	3 (14%)	5 (9%)	0.52
	No	19 (86%)	52 (91)	
Splenectomy	Yes	8 (36%)	9 (16%)	0.05
	No	14 (64%)	48 (84%)	
Gallstone	Yes	0 (0%)	3 (5%)	0.27
	No	22 (100%)	54 (95)	

Discussion

Fetal hemoglobin, or foetal haemoglobin, (also hemoglobin F, HbF, or $\alpha 2\gamma 2$) is the main oxygen transport protein in the human fetus during the last seven months of development in the uterus and persists in the newborn until roughly 6 months old. In newborns, fetal hemoglobin is nearly completely replaced by adult hemoglobin by approximately 6 months postnatally, except in a few thalassemia cases in which there may be a delay in cessation of HbF production until 3-5 years of age. In adults, fetal hemoglobin production can be reactivated pharmacologically which is useful in the treatment of diseases such as sickle-cell disease. (Lanzkron S, 2008).

This study aimed to evaluate the effect of hydroxyurea treatment on fetal haemoglobin level and thus on disease complications in Sudanese patients with sickle cell anaemia. The study included 79 patients; 22 (27.8%) of them were treated by Hydroxyurea and 57(72.2%) were not.

Hb-F level in this study was ranged between 0.9% to 38.5 % (mean 8.4%), this illustrated that Sudanese patients with sickle cell anaemia have low level of Hb-F in comparison to other populations in the region such as Saudi arabia, Kuwait, Qatar, and Bahrain (Mohsen A , 2011). The low level of fetal haemoglobin in those patients may interpret why sickle cell anaemia in Sudan is of the severe type as some studies in some populations with high Hb-F levels have been described as having less severe disease with fewer complications and better survival (Perrine RP, 1978).

Also many other studies in the middle east reported that Hb-F% is elevated in mild sickle cell disease (Ali SA, 1970; Haghshenass, 1977, Perrine RP, 1978).

In contrast, two studies in the United States compared 21 patients manifesting mild sickle cell disease (aged 18-56) with 12 severely affected patients have failed to find these associations between Hb-F% and disease severity. (Steinberg, 1973)

In spite of Hydroxyurea was the first drug to be approved by the FDA for the treatment of patients with moderate and/or severe sickle cell anaemia through the induction of fetal haemoglobin synthesis, our results showed that there is no statistically significant difference in Hb-F level in patients who were treated by Hydroxyurea and those were not (Means: 7.6% and 8.7% respectively, *P,value*: 0.57). This is consistent with study by Fathallah and Atweh who reported that the response to hydroxyurea in sickle cell anaemia patients is variable and about one third of patients with SCD did not respond at all to this treatment (Fathallah H, 2006; Atweh, 2006)

The higher baseline of Hb-F level has been reported to predict better response to hydroxyurea in sickle cell anaemia children.

Comparison of the frequency of disease complications in the last year in the patients who were treated with

hydroxyurea and those were not showed no correlation was found between hudroxyurea administration and disease complications such as pain crisis, dactylitis, leg ulcer, stroke, acute chest syndrome, spleenectomy, and gallstone (*P.value*: 0.61, 0.20, 0.37, 0.13, 0.52, 0.05, 0.27 respectively).

The findings of the present study revealed that hudroxyurea treatment is not the drug of choice for induction of fetal haemoglobin in Sudanese sickle cell anaemia, this can be attributed to many factors reported to influence the response to hydroxurea treatment such as the baseline level of Hb-F as the higher response of Hb-F level has been reported to predict better response to hydroxyurea in sickle cell anaemia children (Steinberg MH, 1997).

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