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(RESEARCH ARTICLE)

Determination of D- dimer level in sickle cell anemia patients under hydroxyurea treatment in Sinnar state, Sudan

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Abstract

Sickle cell disease (SCD) is a group of blood disorders typically inherited from a person's parents. The most common type is known as sickle cell anemia (SCA), is hemoglobin disorders that increase the rate of morbidity and mortality. Aim of this study is to evaluate D- dimer level in patients with sickle cell anemia (SCA) under hydroxyurea (HU) treatment. A total of 90 subjects, Homozygous (SCD) patients (HbSS) treated with Hydroxyurea (HU) (n=30), homozygous (SCD) untreated with hydroxyurea (n=30) and healthy (Hb AA) controls (n=30) matched for age (4 - 20) years, gender and socioeconomic status were enrolled from sinnar pediatric hospital. Venous blood samples 1.8 ml were collected in Trisodium citrate, centrifuged at room temperature then plasma was separated. The effect of the SCD patient's treatment with hydroxyurea on D- dimer level was investigated using Snibe MAGLUMI fully-autochemiluminescence immunoassay (CLIA) analyzer. The results of D-dimer are significantly lower ($0.93 \pm 0.52 \text{ ng/ml}$) (p value 0.000) in (SCD) under (HU) and normal control (0.39 ± 0.14) compared to (SCD) patients without (HU) treatment ($4.61 \pm 1.76 \text{ ng/ml}$). Also, according to clinical status, SCD under HU Treatment about 73% are steady, and crises which about 27 %, SCD without HU treatment steady about 20% and crises about 80%. This reflect the significant role of HU therapy in the beneficial clinical effect. In conclusion, our study revealed low D-dimer levels and improves clinical and hematological characteristic among (SCD) patients under hydroxyurea treatment comparing with (SCD) patient without hydroxyurea treatment, while age showed no effect on the D-dimer levels.

Keywords: SCD; Hydroxyurea; SCA; Treatment; D-dimer

1. Introduction

Sickle cell disease is a chronic hemolytic disorder that is marked by tendency of hemoglobin molecules within red cells to polymerise and deform the red cell into a sickle (or crescent) shape resulting in characteristic vasoocclusive events and accelerated hemolysis [1,2]. Sickle cell crises are characteristic features of disease which include; Vaso-occlusive, Aplastic, infections and hemolytic crises. Chronic hypercoagulable state is generally known to be one of the factors that contribute to vaso-occlusion and progressive end-organ damage in sickle cell disease (SCD) [3,4]. Sickle cell disease (SCD) is a hypercoagulable state. Patients exhibit increased platelet activation, high plasma levels of markers of thrombin generation, depletion of natural anticoagulant proteins, abnormal activation of the fibrinolytic system, and increased tissue factor expression, even in the non-crisis "steady state" [5]. In addition, Studies on SCD patients at steady state patients from different geographic and demographic origins have shown elevated level of markers of coagulation activation [6,7]. One of these marker is D-dimer (fibrin degradation product); a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. Fibrinolysis is the resulting of interactions among multiple plasminogen activators and inhibitors constituting the enzymatic cascade ultimately leading to the degradation of fibrin [8]. It is normally undetectable or detectable at a very low level unless the body is forming and breaking down blood clots as in sickle cell anemia patients. Then, its level in the blood can significantly rise [9]. D-

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dimer levels have certain advantages over other measures of thrombin generation, because it is resistant to ex vivo activation, relatively stable, and has a long half-life [10]. Management of sickle cell anemia is usually aimed at avoiding pain episodes, relieving symptoms and preventing complications. Treatments might include medications and blood transfusions. For some children and teenagers, a stem cell transplant might cure the disease. There are many types of medication used to treatment the sickle cell disease. Hydroxyurea (HU) is a tremendously important drug in the management of patients with (SCD) who have severe clinical manifestations which inhibits ribonucleotide reductase, leading to S-phase arrest of replicating cells, and it is used in(SCD) because of its ability to stimulate production of Hb F [11,12]. The aim of this study is to evaluate D-dimer level in patients with sickle cell anemia (SCA) under hydroxyurea (HU) treatment.

2. Material and methods

This was a hospital based, analytic, descriptive cross-sectional study, conducted in Sudan_ Sinnar state in 2019. A total of 90 subjects, Homozygous (SCD) patients (HbSS) treated with Hydroxyurea (HU) (n=30), homozygous (SCD) untreated with hydroxyurea (n=30) and healthy (Hb AA) controls (n=30) matched for age (4 - 20) years, gender and socioeconomic status were enrolled. Venous blood samples 1.8 ml were collected in Tri soduimcitrae centrifuged at room temperature then plasma was separated. The effect of the SCD patients treatment with hydroxyurea on D- dimer level was investigated using Snibe MAGLUMI fully-autochemiluminescence immunoassay (CLIA) analyzer; Sandwich chemiluminescence immunoassay using ABEI to label an anti-D-dimer monoclonal antibody, and use another D- dimer monoclonal antibody to coat magnetic microbeads. The sample, ABEI label, buffer and magnetic microbeads are mixed thoroughly and incubated at 37C to form a sandwich. After precipitation in a magnetic field, decant the supernatant, and perform awash cycle. Subsequently the starter 1+2 is added to initiate a flash chemiluminescent reaction. The light signal is measured by a photomultiplier within 3 seconds as RLU which is proportional to the concentration of D-dimer present in samples.

2.1. Statistical analysis

Statistical analysis was performed using SPSS (SPSS), data were expressed as mean and standard deviation (M±SD), the means were compared using (one way a nova) and Pearson's correlation analysis was used for correlation of parameters measured, P-value < 0.05 was considered as statistically significant.

3. Results

Our studied group of total SCD patients in Sinnar state - Sudan included (30) under HU treatment Males represent (43%) and (57%) are Females, (30) without HU treatment (50%) Males and (50%) Females and (30) as normal control groups (40%) Males and (60%) Females. The mean age of study groups is (4 - 20years). The mean of D-dimer in study groups are (0.93±0.52ng/ml) in SCD with HU, (4.61±1.76) in SCD without HU that means the D- dimer level was significantly lower among SCD patients under HU treatment (p value 0.000) than SCD without HU as it described in table (1&2). Also, they have been assessed according to clinical status, SCD without HU treatment in crises are more than SCD under HU treatment which reflect the significant role of HU therapy in the beneficial clinical effect explained in Figure (I).

Table 1 Assessment of D- dimer between SCD patients under HU, SCD according to age in Sinnar state -Sudan.

Parameters	4-10Years (Mean±SD)	>10Years (Mean±SD)	P-value
D.dimer in SCD under HU treatment	0.84±0.41	1.01±0.62	0.384
D.dimer in SCD without HU treatment	4.67±2.01	4.51±1.29	0.818

Table 2 Assessment of D- dimer between SCD patients under HU, SCD without HU and control in Sinnar state -Sudan.

Parameters	SCD patients under HU treatment (Mean±SD)	SCD patients without HU treatment (Mean±SD)	Control (Mean±SD)	P-value
D.dimer	0.93±0.52	4.61±1.76	0.39±0.14	0.000

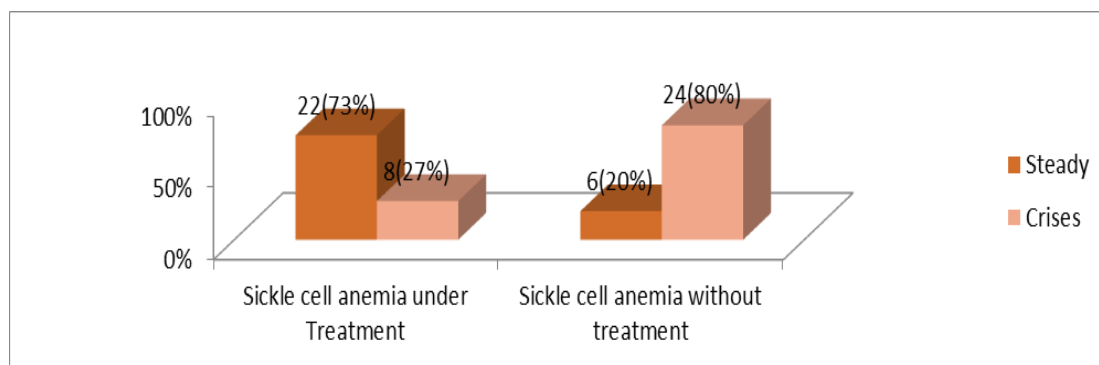


Figure 1 Assessed according to clinical status

4. Discussion

The prevalence rate of sickle cell anemia in Sudan ranging from 2 to 30.4% [13] while western Sudan residents represent the highest prevalence 30% of SCA in Sudanese population [14,15,16]. And 16% among immigrants from Blue Nile [17]. There are many studies conducted in Sudan among patients with sickle cell anemia [1,18]. Our study is first study in conducted in Sudan to determine the effect of hydroxyurea (HU) medication among patients suffering from sickle cell disease.

Although SCD is characterized by hypercoagulability [19, 20]. the contribution of coagulation to disease pathophysiology remains poorly defined. D-dimer is increased in patients with SCD during the non-crisis, “steady state” and is further increased during acute pain episodes [21]. D-dimer levels are reported to correlate with the frequency of pain episodes measured during the following year [18]. As well as the interval for development of pain episodes, suggesting that coagulation activation may contribute to vaso-occlusion in SCD [21]. There are conflicting reports regarding further increases in coagulation activation markers during painful crises as compared with the non-crisis, ‘steady-state’ [22]. There are also conflicting reports on the association between markers of coagulation activation and the frequency of painful crisis. A significant correlation was reported between D-dimer levels measured during the non-crisis state and the frequency of pain crises the following year in addition, plasma D-dimer level was inversely correlated with the time to the next pain episode [23]. In this study we found low levels of plasma D-dimer ($p = 0.00$) among SCD patients under HU comparing with SCD patient without HU treatment, this finding was consistent with several studies like Denis Noubouossi et al [24,25]. Also, as in our result samir K ballas et al conclude that the treatment of SCD patients with HU improves their clinical and hematological characteristic due to response of Hb F to HU treatment [26]. Also, on other hand there are agree with our study in interval of blood transfusion, they found that in SCD patients under HU treatment there are decrease in frequency of blood transfusion [27]. our study has some limitations, such as the relatively small number of subjects. Our finding on these results must be determined in further large controlled studies. Also, we are not considered the other disorder than SCD like liver disease and other disease that can change blood coagulation [28]. Also, another limitation in our study it should including other biomarkers, such as interleukins or Thrombin generation assays.

5. Conclusion

In conclusion, our study revealed low D-dimer levels and improves clinical and hematological characteristic among SCD patients under hydroxyurea treatment comparing with SCD patient without hydroxyurea treatment, while age showed no effect on the D-dimer levels.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interests between authors.

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