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Coagulation and RBC Parameters for Sickle Cell Anemia Patients in Painful Crisis and Steady State Conditions: A Cross Sectional Study from Makkah City, Saudi Arabia

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Abstract: ***Introduction*: Sickle cell anemia (SCA) is one of the common hematological disorders found worldwide. Determination of the difference between steady state and sickle cell crisis in term of coagulation andred cellsparameters can help clinicians to assess patients'condition and management. *Methods*: A total number of 95 SCA patients were recruited in this study including 45 females and 50 males aged between 13 and 53 years old. These were divided into steady state and sickle crisis. Complete Blood Count and coagulation profile were performed to determine anemia status and assess the hypercoagulability status in steady state and sickle crisis. *Results*: 50 (52%) patients were diagnosedwith crisis, while 45 (47%) patientswere found in steady state. Sickle cell crisis was more common in the age of 20 to 30 years (n=23; 24.21%) than other age groups. No statistical significance was observed in coagulation and red cells profiles except in the red cell hemoglobin contents represented by MCH (P=0.04) and MCHC (P=0.004) between SCA with crisis and a steady state. *Conclusion*: There was no statistical significance found in the coagulation profile between the two conditions. Hyperactivity of coagulation cascade cannot be ruled out and more laboratory tests such as D-dimers, proteins C and S measurements should be performed to confirm this finding. Our study concluded thatthe significant increase in MCH and MCHC may occur due to the release of endogenous iron from the broken hemoglobin giving a significant contribution to polymerization and crisis process.***

Keywords: Sickle Cell Anemia, Coagulation profile, RBC parameters, sickle cell crisis, steady state

1. Introduction

Sickle cell disease (SCD) is a commonhematological disorder affecting millions of individuals annually and inherited in an autosomal recessive manner. It is caused by a point mutation that affect the β-globin gene *(HBB)*resulting in abnormal Hb known as sickle hemoglobin (HbS). Homozygous mutation leads to expression of two copies of β^Swhich in turn result inSickle Cell Anemia (SCA) while heterozygous mutation leads to one copy formation of β^Sresulting in a milder form known as Sickle Cell Trait (SCT)[1]. Compound heterozygous mutations, where two different mutant alleles at the β-globin locus, are commonly encountered worldwide resulting in SCD. The SCA is characterized by severe clinical symptoms and deformation of regular biconcave shaped erythrocyte to more rigid sickle shaped due to theHbS formation[2]. In Saudi Arabia, the first case of SCD was reported in the Eastern province in the 1960s [3]. The prevalence of SCD in Saudi Arabia varies between different regions of the country where the Eastern province harborsthe highest number of affected individuals reaching about 17% for SCT and 2.6% for SCD[4, 5].SCA is commonly associated witha hypercoagulable state that leads to morbidity events such as vaso-occlusive and cerebrovascular accidents [6]. Such events are exaggerated with a decrease level of natural anticoagulant proteins caused by chronic consumption due to increase thrombin generation in the vascular endothelium resulting vaso-occlusive painful episodes, stroke, and acute chest syndrome[7, 8]. Hypercoagulability state in SCA patients is characterized byan increase in the thrombin generation, platelet activation, and reduced natural anticoagulants such as proteins C and S. It results from the short survival of platelets with increase in the level of adenosine diphosphate along with decreased level of anticoagulants such as protein C and S [9].Determination of changes in coagulation factors can be used to predict the clinical outcome in SCA patients. For example, an increase in fibrinolytic activity related to increase in the frequency of painful episodes. This increase in fibrinolytic activity is a result of inhibition binding of protein S to β-2 glycoprotein 1 by antiphospholipid antibodies. In addition, some SCA patients with strokes and vaso-occlusion crisis have a high level of thrombin and prothrombin [10].During steady state, many Sickler patients show no clinical symptoms reflecting good health condition. However, this state can be interrupted by painful episodes and vaso-occlusive crisis (VOC)[11]. Recognition of the patient's steady state makes the clinical and hematological assessment easy. In SCA, steady state is defined as a condition where thepatients do not show signs of infection, acute clinical symptoms or crisis for at least three months [12]. On the other hand, sickle crisis is defined as episodes of acute illness that require an immediate medical attention and treatment such as analgesic drug ingestion and blood transfusion [13]. Determination of hematological parameters differences between steady state and sickle cell crisis is important for early recognition and clinical priority assessment. Thus, the aim of this work is to determine the hematological valuesand variation of red cell parameters and coagulation profile in steady state and crisis of SCA

patientswho visited and admitted to Al-Noor Specialist Hospital, Makkah, Western province of Saudi Arabia. The outcome of this study will determine the base line value of these parameters and can be used to assess and evaluate clinical severity of the SCA patients.

2. Methods

The study was conducted in Al-Noor Specialist Hospital, Makkah, Saudi Arabia. The hospital is a tertiary health care level hospital in Makkahwhere SCA patients are gettingclinical management in the emergency room or medical ward.Patients data wereobtained from the laboratory database after getting ethical permission from the hospital administration to conduct the study (approval no. 61147, 2/12/1436). Atotal number of 95 SCA patients wererecruited in this study including 45 females and 50 males aged between 13 and 53 years old age. The number of SCA patients with sickle cell crisis is 50, while the number of SCA in a steady state is 45. The clinical observation of SCA patients were clinically diagnosed by specialists and consultants in the ER and medical ward.Complete Blood Count was measured using XN-1000™ Hematology Analyzer (Sysmex, Lincolnshire, USA). This include Hemoglobin (Hb), Mean Cell Volume (MCV), Mean Cell Hemoglobin (MCH), and Mean Cell Hemoglobin Concentration (MCHC) and Platelet count. Coagulation profile including Prothrombin Time (PT), International Normalization Ratio (INR) and Activated Partial Thromboplastin Time (aPTT) were measured using STA Compact Max® (Stago, Parsippany, USA). Data analysis and statistical significance calculation were done using Excel 2010 to compare the mean values of coagulation and hematological parameters variation in steady and crisis states

3. Results

A total number of 95 SCA patients were recruited in this studywhere45 (47%) patients were found to be in a steady state while the remaining 50patients (52%) were diagnosed with crisis. Demographic data of the SCA patientsis shown in Table 1. The mean age of SCA patient in the steady state is 25.4 years ± 8, while in crisis is 26.4 years ± 7.7. Regarding the gender, 28 (29.47 %) male and 17 (17.89 %) female in the steady state, while those in crises are 24 (25.3 %) male and 26 (27.4 %) female. Most patients (n=46 – 48%) are within the age category of 20 – 30 years indicating that young adult patients require more clinical attention and follow up.

Coagulation profile of the patients is illustrated in Table 2. There is no significant difference in coagulation screening parameters between the steady and crisis states. PT, INR, aPTTand platelets count areall within normal range. This means that both primary and secondary coagulation are all maintained and tolerated in both conditions.Hemoglobin level and red cell indices of the patients with crisis and steady state are shown in Table3. There is a significance difference in MCH and MCHC between crisis and steady states, indicating a decrease in the hemoglobin content of the RBCsdue to the stress condition caused by sickle crisis. Other parameters including Hb and MCV did not show any significance difference.

4. Discussion

The aim of this study is to find the difference in coagulation and anemia parameters between steady state and crisis conditions in a cohort of Saudi SCA patients. Our work showed that there is no significance difference in all measured parameters except in the red cell hemoglobin contents represented by MCH and MCHC between SCA with crisis and the steady state.This is contradictory to previous studies where coagulation profile was found to be significantly prolonged in crisis condition compared to the steady state[14, 15].An early study performed by Richardson*et al*[14] found that SCA patients showed platelet and coagulation activation more pronounced with significant difference in crisis than in steady state.Raffiniand his colleagues [15]found that children with SCD admitted for surgical procedures were more likely to have prolonged coagulation screening profile than those tested at a well visit. Furthermore, Chinawa *et al*[16]found that children with SCA in crisis showed prolonged PTT compared with a steady state. This could be due to the effect of cytokine and anti-lupus factor production during infection, which will lead to consumption of the intrinsic factors [16, 17]. Regardingour study, although the increase in the platelets counts detected in all patients was not statistically significant, this increase may reflect the hyperactivity status that is commonly seen in SCA. Kenny *et al*[18]performed a study about platelets hyperactivity on SCA patients. They found that there was a significant increase in the platelet counts due to autosplenectomy, which results to increase in the population of young metabolically active platelets. Furthermore, SCA children patients showed similar result of increasing in platelets count in both crisis and a steady state [16].The hematological values of our SCA patients showed that there is a significance difference in MCH and MCHC, $p < 0.05$ and $p < 0.005$ respectively, in crisis than the steady state. This is consistent with the study performed by Omoti[19]. The study concluded that SCA with crisis have high MCHC due to the release of endogenous iron from the broken hemoglobin and the high MCHC may predispose to polymerization and crisis. However, our results of MCV values of adult SCA patients do not show any statistically difference between crisis and a steady state. This is contrast to the finding of Omoti, who found that there is increase in MCV value in SCA with crisis due to the stimulation of hemopoisis in crisis than a steady state of SCA [19]. Furthermore, the reduced values of MCHC and MCH is related to the effect of anemia of chronic disease, infection and hemolysis [20]. In conclusion, the present study indicates that SCA adult patients showed increase in coagulation profile in both crisis and the steady state compared to the normal control. This is due to the hyperactivity condition caused by eithervascular stasis or endothelial damage during crisis or due to platelet activation that occur during the steady state that contributes to the onset of vaso-occlusive crisis. The finding of this study can be used as prognostic parameter for crisis in SCA patients.

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Table 1: Demographic picture of SCA patients during steady state and crisis condition

Age	Steady state; n (%)	Crisis; n (%)
< 20	10 (10.52%)	11 (11.57%)
20 – 30	23 (24.21%)	23 (24.21%)
31 – 40	10 (10.52%)	15(15.78%)
> 40	2 (2.10%)	1 (1.05%)

Table 2: Comparison of mean values of coagulation parameters for SCA in crisis and steady state

Coagulation parameter	Sickle crisis (mean value)	Steady State (mean value)	*p* value	Control	Reference range
PT (Sec)	12.74 ± 1.4	12.85 ± 1.4	0.35	11.9 ± 0.7	11-16 Sec
INR	1.11 ± 0.1	1.11 ± 0.1	0.42	1 ± 0.07	0.6 - 1.2
PTT (Sec)	31.83 ± 6.4	31.15 ± 6.2	0.3	40.5 ± 5.5	27-39
Platelets Count (X 10^3/µl)	463.44 ± 242.5	445.68 ± 174.1	0.34	270 ± 47.8	150-400

Table 3: Comparison of mean values of hematological parameters for SCA in crisis and staedy state

Hematological parameter	Sickle crisis (mean value)	Steady State (mean value)	p value	Control	Reference range
Hb (g/dl)	8.32 ± 1.56	8.30 ± 1.41	0.48	14.15 ± 1.18	Male: 13-17 Female: 12 - 15
MCV (fl)	80.31 ± 10.98	82.87 ± 10.23	0.12	87.95 ± 3.13	80-101
MCH (pg)	27.14 ± 1.63	28.68 ± 4.24	0.04	28.9 ± 1.12	27-32
MCHC (g/dl)	33.63 ± 1.63	34.51 ± 1.57	0.004	32.9 ± 0.66	31.5-34.5