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Haematological Parameters of Sickle Cell Disease Patients with Menstruation Induced Vaso-Occlusive Crises

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Abstract: This study evaluated the premenstrual and menstrual haematological parameters of female SCD patients with menstruation induced Vaso-occlusive Crises (VOC) with the aim of identifying any significant changes that might be etiologically associated with the crises. Fifteen female patients with sickle cell anemia (Hb SS) and history of menstruation induced VOC were studied along side equal number (15) of age and sex matched patients without history of menstruation induced VOC. Patients without history of menstruation induced VOC had mean premenstrual values of haematocrit, total leucocyte count and platelet count of 0.26 L L^{-1}, 12×10^{1} L^{-1} and 458×10^{9} L^{-1}, respectively, which were not significantly different from the corresponding mean menstrual values of 0.25 L L^{-1} for haematocrit, 11.5×10^{9} L^{-1} for total leucocyte count and 452×10^{9} L^{-1} for platelet count ($p>0.05$). Patients with history of menstruation induced VOC had mean premenstrual values of haematocrit and total leucocyte count of 0.25 L L^{-1} and 11.8×10^{9} L^{-1}, respectively, which were not significantly different from the corresponding mean menstrual values of 0.24 L L^{-1} for haematocrit and 12.3×10^{9} L^{-1} for total leucocyte count ($p>0.05$). However, the mean menstrual platelet count of 605×10^{9} L^{-1} was significantly higher than the mean premenstrual value of 452×10^{9} L^{-1} ($p<0.05$). This data would suggest that high menstrual platelet count was aetiologically associated with the development of menstruation induced VOC. There is therefore the need to investigate a possible beneficial role of low doses of anti-platelet agents in preventing or managing menstruation induced VOC.

Key words: Vaso-occlusive, sickle cell anemia, menstruation, haematological parameters

INTRODUCTION

Sickle Cell Disease (SCD) is a constellation of inherited structural disorders of haemoglobin, which are characterised by red cell sickling and associated clinical features. The commonest form of SCD is sickle cell anaemia in which the sickle β-globin gene is inherited in a homozygous state (HbSS) (Davies and Oni, 1997; Flint *et al*., 1993). Other forms of SCD include compound heterozygous states for the sickle cell β-globin gene and genes for HbC (HbSC), β-thalassemia (HbSβ-thal), HbD (HbSD), HbO (HbSO) and HbLepore (HbSLepore) (Davies and Oni, 1997; Flint *et al*., 1993). The Hb SS is the commonest form of SCD in Nigeria where it affects 2-3% of the general population (Akinkugbe, 1992). The sickle cell β-globin gene is widely spread throughout Africa, the Middle East and Asia and by population movement to the Caribbean, North America and Northern Europe (Davies and Oni, 1997). The frequency of sickle cell carriers (HbAS) is up to 20-25% in West Africa including Nigeria and the frequency has reached high levels in these populations because the carrier state protects against malaria infection (Davies and Oni, 1997; Akinkugbe, 1992; Hood, 1996).

The clinical presentation of SCD is due to vaso-occlusive episodes resulting from polymerization of deoxygenated haemoglobin S leading to the characteristic change in shape of erythrocytes to a crescent or sickle shape (Davies and Oni, 1997). Further more, recent studies suggest that sickled erythrocytes increase vascular endothelial production of adhesions molecules which creates a situation that favors intravascular cellular adhesions, stasis and prolongation of blood flow transit time, thereby increasing the chances of intravascular

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microthrombi formation (Shia *et al*., 2000). These events eventually lead to blockade of small blood vessels resulting in tissue infarctions, which present clinically as the characteristic painful Vaso-Occlusive Crises (VOC) that commonly affect the bone. Crises are usually precipitated by infections, dehydration or extreme weather conditions (Brozovic *et al*., 1987). There is no established relationship between VOC and menstruation. Nonetheless, in our hospital we have had to manage a number of cases of VOC that were apparently precipitated by normal monthly menstruations in young female patients with SCD.

In this research we evaluated the haematological parameters of female SCD patients with menstruation induced VOC with the aim of identifying any significant changes that might be etiologically associated with the crises in such patients as seen at the Federal Medical Centre, Birnin Kudu, Northwest Nigeria.

MATERIALS AND METHODS

Fifteen female patients with sickle cell anemia (Hb SS) and history of menstruation induced VOC were studied along side equal number (15) of age and sex matched patients without history of menstruation induced VOC. Medical records of the patients with history of menstruation induced VOC revealed that each patient had 3-7 menstruations that were associated with VOC in the year preceding this study. In each case the VOC usually started within 24-48 h after onset of bleeding and tailed off after the last day of bleeding. All of the patients studied in this work were spinsters with no previous history of pregnancy and were not on any intra-uterine or hormonal contraceptives.

The patients studied in this report were confirmed cases of sickle cell anemia (Hb SS) based on positive sickling tests and haemoglobin electrophoresis at a pH of 8.6 on cellulose acetate paper. After due consent, the patients were followed up for a period of 1 year (June 2004-May 2005). For each patient, the age and age at menarche were recorded and the menstrual cycles were observed throughout period of study during which premenstrual and menstrual values of haematocrit, total leucocyte count and platelet count were also evaluated. Premenstrual values were determined on daily basis during the seven days that preceded menstruation, while the menstrual values were determined on daily basis during the days of menstruation. The haematocrit, total leucocyte count and platelet count were estimated by standard manual techniques (Dacie and Lewis, 1991). The premenstrual and menstrual mean values of haematocrit, total leucocyte count and platelet count were statistically compared among patients with history of menstruation induced VOC and those without history of menstruation induced VOC based on Student t test and a probability level of $p<0.05$ was taken as significant.

RESULTS

Patients with menstruation induced VOC had a mean age of 22 years, attained menarche at a mean age of 14 years and had a mean duration of menstrual bleeding of 3.5 days during the period of study. Patients without history of menstruation induced VOC had mean age of 23 years, attained menarche at a mean age of 13 years and had a mean duration of menstrual bleeding of 4 days, which did not differ significantly ($p>0.05$) from the corresponding values for patients with history of menstruation induced VOC. The premenstrual and menstrual values of haematocrit, total white cell count and platelet count for patients with history of menstruation induced VOC as well as those without history of menstruation induced VOC are shown on Table 1.

Patients with history of menstruation induced VOC: The mean premenstrual haematocrit was 0.25 $L\ L^{-1}$, which was not significantly different from the mean menstrual haematocrit value of 0.24 $L\ L^{-1}$ ($p>0.05$). Similarly the mean premenstrual total leucocyte count of $11.8\times10^{9}\ L^{-1}$ did not significantly differ from the mean menstrual total leucocyte count of $12.3\times10^{9}\ L^{-1}$ ($p>0.05$). However, the mean menstrual platelet count of $605\times10^{9}\ L^{-1}$ was significantly higher than the mean premenstrual value of $452\times10^{9}\ L^{-1}$ ($p<0.05$).

Patients without history of menstruation induced voc: The mean premenstrual values of haematocrit, total leucocyte count and platelet count were 0.26 $L\ L^{-1}$, $12\times10^{9}L^{-1}$ and $458\times10^{9}L^{-1}$, respectively, which were not significantly different from the corresponding mean

Table 1: Haematological parameters of sickle cell anaemia patients with and without menstruation induced vaso-occlusive crises

Parameters	Premenstrua values	Menstrual values	Statistical significance
Patients with menstruation			
Haematocrit ($L\ L^{-1}$)	0.25±0.04	0.24±0.03	p>0.05
Total leucocyte count ($x10^{9}\ L^{-1}$)	11.8±3.0	12.3±4.0	p>0.05
Platelet count ($x10^{9}\ L^{-1}$)	452.0±50.0	605.0±55.0	p<0.05
Patients without menstruation			
Haematocrit ($L\ L^{-1}$)	0.26±0.04	0.25±0.03	p>0.05
Total leucocyte count ($x10^{9}\ L^{-1}$)	12.0±3.0	11.5±4.0	p>0.05
Platelet count ($x10^{9}\ L^{-1}$)	458.0±50.0	452.0±50.0	p>0.05

menstrual values of 0.25 $L\ L^{-1}$ for haematocrit, $11.5\times10^{9}\ L^{-1}$ for total leucocyte count and $452\times10^{9}\ L^{-1}$ for platelet count ($p>0.05$).

DISCUSSION

The finding of low haematocrit values of between 0.2 to 0.3 $L\ L^{-1}$ with no significant differences between premenstrual and menstrual values among our patients was consistent with the fact that patients with SCD generally have a background rate of red cell sickling, which drastically shortens the life span of red cells leading to a chronic haemolytic anaemia and jaundice even in steady state (Kaul *et al*., 1996). The lack of significant difference between premenstrual and menstrual mean haematocrit values in SCD patients with and those without history of menstruation induced VOC would suggest that both groups of patient had normal menstruations with no excessive blood loss. However, the haematological parameters of our patients revealed marginally raised mean values of total leucocyte count with no significant differences between premenstrual and menstrual values in patients with and those without history of menstruation induced VOC. This finding is in keeping with earlier studies, which showed that a modest leucocytosis is a common feature of SCD and was thought to be due to redistribution of granulocytes from marginal pool to the circulating pool (Boggs *et al*., 1973).

The premenstrual and menstrual mean platelet counts were high in patients with and those without history of menstruation induced VOC. The finding of high platelet counts in SCD patient is consistent with earlier studies, which showed that thrombocytosis was common in SCD and was attributed to the background haemolytic anaemia and the auto-splenectomy associated with the disease (Freedman and Karpatkin, 1975; Schwartz, 1972). Nonetheless, there was no significant difference between premenstrual and menstrual mean values of platelet count among SCD patients without history of menstruation induced VOC. This is in contradistinction from the values obtained in patients with history of menstruation induced VOC in whom the menstrual mean platelet count was significantly higher than the premenstrual value. However, there was no obvious reason for the higher menstrual platelet count among SCD patients with history of menstruation induced VOC. One possible explanation could be that this group of patients has exaggerated response to normal menstruation bleeding, which led to reactive thrombocytosis. Previous studies have shown that blood loss was an important cause of reactive thrombocytois (Buss *et al*., 1994). Present finding could be further interpreted to suggest that raised platelet count would lead to higher blood viscosity, which can precipitate VOC. This is because previous studies had shown that whole blood viscosity was an important factor in the pathogenesis of VOC in SCD (Schmalzer *et al*., 1987). More over, once VOC is initiated, previous reports suggested that sickled red cells cause widespread microvascular blockade and endothelial damage leading to exposure of collagen (Mehta and Mehta, 1979). Collagen exposure would result in activation of platelet and clotting factors, which will lead to intravascular platelet aggregation and fibrin deposition (Mehta and Mehta, 1979). This chain of events will increase vascular blockade and set up a vicious cycle by causing tissue hypoxia that will in turn lead to more red cell sickling and crises. The finding in this study would therefore suggest that high menstrual platelet count was aetiologically associated with the development of menstruation induced VOC.

It is not possible, within the scope of this study, to determine the reason why female SCD patients with history of menstruation induced VOC mounted an exaggerated reactive thrombocytosis in response to normal menstrual blood loss. There is obviously the need for more studies on this subject matter, which may include detailed analysis of the hormonal changes that occur during the menstrual cycle.

CONCLUSIONS

The data from this study would suggest that raised platelet count due to reactive thrombocytosis, probably resulting from exaggerated response to menstrual blood loss, was the cause of menstruation induced VOC in female patients with SCD. There is the need for more elaborate studies to find out if certain hormonal factors contribute to the development of this problem. There is also the need to investigate a possible beneficial role of low doses of anti-platelet agents in preventing the occurrence or decreasing the severity of this problem in affected patients.

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