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**EFFECT OF BLOOD TRANSFUSIONS AND NON -TRANSFUSION ON SERUM FERRITIN LEVELS
OF PATIENTS WITH SICKLE CELL DISEASE ATTENDING THE PAEDIATRIC HAEMATOLOGY
CLINIC OF THE UNIVERSITY OF BENIN TEACHING HOSPITAL**

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ABSTRACT:

The need for recurrent blood transfusion is thought to be protective against iron deficiency in children affected by sickle cell disease. However, the subject has not received sufficient attention in Nigeria. The objective of the study was to assess the iron status of transfused and non transfused sickle cell disease children aged 1-18 years who are in steady state, using serum ferritin levels. In this cross-sectional study, 100 children with sickle cell disease aged 1-18years attending the Paediatric Haematology Out-Patient Clinic were recruited consecutively. The subjects were in steady state and had not received blood transfusion in the last 3 months. Their iron status was determined using serum ferritin levels. Serum ferritin levels of <25ng/ml was used to establish the presence of low iron stores. A patient with low mean corpuscular volume for age together with low serum ferritin (<25ng/ml) was considered to have iron deficiency anemia (IDA). Fifty four (54%) of the 100 subjects had received blood transfusion. The lowest mean serum ferritin value of 34 ± 36.1 ng/ml was seen amongst subjects who had never received blood transfusion in the past. The prevalence of iron deficiency was 35.2% and 60.1% in transfused and non transfused SCD children respectively. The prevalence rates of iron deficiency anemia (IDA) were 14.8% and 30.4% respectively in transfused and non transfused SCD children. The prevalence of iron deficiency increased with the duration of blood transfusion. 20.8% of those who had received blood transfusion less than a year prior to the study were iron deficient while 85.7% of those who received blood more than 5 years prior to the study were deficient. This difference was statistically significant. Iron deficiency and iron deficiency anemia were seen in transfused and non transfused SCD children but the prevalence was higher in the non-transfused group. Transfusion given more than 5 years ago, was not protective against the presence of iron deficiency.

Key words: Sickle cell disease, children, serum ferritin, iron deficiency, iron deficiency anemia

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INTRODUCTION:

Sickle cell disease (SCD) is the commonest haemoglobinopathy in Nigeria with prevalence as high as 3% in the newborn population [1]. The disease is associated with chronic haemolysis resulting in anemia [2]. Other haematologic complication of the disease like aplastic anemia, hyper-haemolysis (usually following infections) and sequestration crisis often worsen the anemia resulting in the need for blood transfusion [2,3,4]. In a study of 131 SCD children aged 9months to 15 years in Western Nigeria, 43.5% had received blood transfusion and 57% of those transfused had had multiple transfusions [5]. In the management of certain complications of SCD like stroke, priapism, and acute chest syndrome, repeated blood transfusions are usually advocated [6]. As a consequence, SCD children are highly predisposed to the need for recurrent blood transfusions. Transfusions should protect the SCD child from developing iron deficiency anemia as each unit of blood delivers 200 g of iron to the recipient [7].

One major complication that may arise from frequent transfusions is iron overload. The diagnosis of iron deficiency or overload is based largely on laboratory assessment [8,9]. The routine blood investigations done in most health facilities is not able to detect iron

overload and may only suggest the presence of iron deficiency. This is because mean corpuscular volume (MCV) is 97% specific for the diagnosis of iron deficiency [9]. Various studies [9, 10] have shown a good correlation between serum iron and body iron stores even amongst SCD patients. This is because serum iron levels are roughly proportional to total iron stores. In a study carried out by Vichinsky et al [9] involving the use of several forms of tests to determine iron status in SCD patients, serum ferritin measurement <25ng/ml was most specific for iron deficiency. In that study, there were no false positive results with the use of this method. In Nigeria, most health facilities lack the laboratory facilities required for routine assessment of iron status in these children. The above reason prompted the present study.

The main purpose of our study is to assess the iron status of transfused and non-transfused SCD children using their serum ferritin levels as criteria. Other objectives of the study were to describe the frequency of blood transfusion and the effect of interval of blood transfusion on iron status.

PATIENTS AND METHODS:

This cross-sectional study was conducted between May and June 2009. One hundred SCD children attending the Consultant Out

Patient Clinic (Paediatric Haematology) of the University of Benin Teaching Hospital were studied. The subjects were aged 1-18 years, and were in steady state of health. A patient is said to be in steady state if he/she is afebrile, and free of complications at the time of sampling. Patients who had received blood transfusion in the last 3 months prior to the study were excluded. Five millilitres of blood was collected by venepuncture. Haemoglobin concentration (Hb), packed cell volume (PCV), and mean corpuscular volume (MCV) were assessed using the Abacus junior model automated analyser [11], reticulocyte counts were done using microscopic viewing after staining with brilliant cresyl blue solution and serum ferritin was done using the Ferritin Quantative Test Kit (a solid phase enzyme-linked immunosorbent assay) with the optic density of each sample determined by the Chemware microtitre reader (Awareness Technology USA 2006 Model).

A subject was classified as iron deficient (reduced iron stores) if the serum ferritin is <25ng/ml, and those with co-existing low MCV for age (0.5-2years<70fl, 2-5yrs <73fl, 5-9yrs<75fl, 9-14yrs<76fl, 14-18<77fl) [12] were classified as having iron deficiency anemia (IDA). Patients with serum ferritin levels higher than normal for age were classified as having iron overload.

Ethical approval was obtained from the Ethic and Research Committee of the University of Benin Teaching Hospital. Informed consent was obtained from the patients and /or their parents/caregivers.

The data obtained was analysed using the statistical package for Social Sciences (SPSS) software package version 13.

Values were expressed as means and standard deviation. The student's T-test was used to compare means and Chi square was used to compare proportions. Fisher's exact test was used to compare frequencies when the cell value was less than 5.

RESULTS:

A total of 100 SCD children age 1-18 years in steady state were recruited into this study. They were made up of 60 males and 40 females. The mean age of all the children was 7.7 ± 4.8 years with a median of 6.5 years. Ninety seven (97%) of them were haemoglobin (Hb) SS whilst the remaining 3 (3%) were HbSC.

Fifty four (54%) of these children had received blood transfusion. Of these, 18 (33.3%), 15 (27.8%), and 21 (38.9%) had received one, two or more than 3 transfusions respectively in the past.

Haematological parameters of transfused and non transfused subjects:

Table 1 shows the haematological parameters of the transfused and non-transfused subjects. The serum ferritin level was higher in the transfused than non transfused subjects but this difference was not significant. There was no statistical significant difference in the other parameters above between the transfused than non transfused subjects. Of the 54 patients who had been transfused, 19 (35.2%) had low serum ferritin. Of these, 11(20.4%) had serum ferritin levels less than 25ng/ml (iron deficiency) but had normal MCV, while 8 (14.8%) had low serum ferritin and low MCV for age showing the presence of IDA. None of 54 transfused patients had levels above normal for age. While of the 46 who had never been transfused, 28 (60.3%) had serum ferritin less than 25ng/dl. Of these, 14 (30.4%) had iron deficiency (low serum ferritin only) while 14 (30.4%) had IDA (low serum ferritin and low MCV for age). None had iron overload.

The prevalence of iron deficiency (reduced iron stores) in the transfused and non transfused patients was therefore (19/54) 35.2% and (28/46) 60.9% respectively (Table 2). This difference was statistically significant ($p=0.016$, OR =1.7).The prevalence of IDA was (8/54) 14.8% and (14/46)30.4% in the transfused and non transfused patients respectively. The lowest mean serum ferritin value of

34 ± 36.1 ng/ml was seen among subjects who had never been transfused. The mean serum ferritin level was higher in patients with 2 transfusions than patients with ≥ 3 transfusions (Table 3). The difference in the mean serum ferritin levels in the subjects who had never been transfused and those who had received one, two and three or more transfusions was not statistically significant ($p=0.31$).

Number of blood transfusions and iron status of the study population:

Iron deficiency was highest (60.9%) in subjects who had not received any previous blood transfusion (Table 4).

Interval since last blood transfusion and iron status of the subjects:

There was a statistically significant association between the period preceding the last blood transfusion and the presence or absence of iron deficiency ($p=0.002$).

The prevalence of iron deficiency increased as the time interval between the last blood transfusion and the study period increased. Five (20.8%) of twenty four subjects who had been transfused in the last one year were iron deficient while six (85.7%) of the seven subjects who had been transfused for more than five years preceding the study iron deficient (Table 5).

Table 1: Hematologic parameters of transfused and non transfused subjects

Laboratory parameters	Previous Transfusion		t	p-value
	Yes (Mean±SD)	No (Mean±SD)		
Packed Cell Volume (%)	22.3±3.2	23.2±3.8	1.29	0.20
Mean Corpuscular Volume (fL)	77.9±9.3	74.9±8.5	1.70	0.10
Haemoglobin concentration (g/dl)	7.4±1.1	7.6±1.2	0.87	0.39
Reticulocyte count (%)	2.5±1.5	2.6±1.4	0.34	0.73
Serum Ferritin (ng/ml)	46.9±35.2	34.0±36.1	1.85	0.07

Table 2: Iron status in transfused and non-transfused subjects

Iron Status	Previous blood transfusion	
	Yes: n = 54 (%)	No: n = 46 (%)
Deficiency	19 (35.2)	28 (60.9)
Normal	35 (64.8)	18 (39.1)
Overload	0	0

p=0.016; OR = 1.7

Table 3: The mean serum ferritin levels according to the number of previous blood transfusions

No of previous transfusions	No of subjects	Mean serum ferritin (ng/ml)
None	46	34.0±36.1
Once	18	43.5±39.6
Twice	15	52.1±34.9
≥three times	21	46.0±33.0

p = 0.31

Table 4: Number of previous blood transfusions and the iron status of study subjects

No of blood transfusions	Iron status		Total N(%)
	Deficient n (%)	Normal n (%)	
None	28(60.9)	18 (39.1)	46(100)
Once	8(44.4)	10 (55.6)	18(100)
Twice	4(26.7)	11(73.3)	15(100)
≥ Three times	7(33.3)	14 (66.7)	21(100)

$$\chi^2 = 7.7, df=3, p=0.05$$

Table 5: Comparison of interval between last blood transfusion and iron status

Time interval α (years)	IRON STATUS			p-value	OR
	Deficiency N(%)	Normal N(%)	Total N(%)		
<1	5(20.8)	19(79.2)	24(100)	0.08	0.5
1 – 2	3(25.0)	9(75.0)	12(100)	0.51	0.7
3 – 4	5(45.5)	6(54.5)	11(100)	0.49	1.4
>5	6(85.7)	1(14.3)	7 (100)	0.006	3.1

$$\chi^2=11.1, df=3, p=0.001 \quad \alpha = \text{interval between last transfusion and time of study}$$

DISCUSSION:

Blood transfusion was common among our patients with SCD. This is not surprising as similar finding has been reported from a previous study in Nigeria [5]. In two separate studies in Senegal, of the 323 SCD children

aged 5months to 22 years and 60 SCD patients studied, 30% and 30.7% respectively had received blood transfusion [13,14]. In 186 Congolese SCD subjects aged 1-21 years, 80.6% had been transfused [15]. In Yemen, in a study of 75 HbSS patients aged 1-30 years,

41.3% had been transfused [16], while 54.3% of the 70 SCD patients aged 1-30 in the US had been transfused [9]. In Jamaica, in a study of 311 subjects, 70.6% had received at least one transfusion by the age of 20 years [17]. In another study in Brazil on 135 SCD children less than 2 years old, 12.6% had been transfused [18]. The prevalence is much lower in the Brazilian study because of the younger age of the children studied. Exposure to blood transfusion is thus a common occurrence globally although the indication for this may vary from country to country based on the preferred pattern for treatment of the various forms of crisis in SCD children and the availability of blood for transfusion.

In this study, the haematologic parameters were similar in the transfused and non transfused SCD patients. Vichinsky et al [9] noted a significant difference in the MCV level of the transfused and non transfused children. The transfused HbSS had higher MCV compared to the non-transfused HbSS patients and the mean Hb concentration was higher in the transfused group compared to the non-transfused group although it was not stated how often and how recent before the study these patients were transfused.

Iron deficiency is a spectrum; the earliest stage is depletion of iron stores which is characterized by low serum ferritin levels. The most severe form is the iron deficiency anemia (IDA) and is

characterized by low MCV and low serum ferritin levels. The prevalence of iron deficiency anemia (IDA) in the transfused and non transfused group in this study was 14.8% and 30.4% respectively. This is much higher than the 1.7% in Senegalese SCD children [14] and the 5.9% and 19.5% in the transfused and non transfused SCD children in Brazil [18] and the 3.2% and 20.5% in transfused and non transfused Yemen SCD patients [16].

In Jamaica, the prevalence of iron deficiency anemia was 8.5% amongst transfused SCD subjects [19], while in the USA, prevalence of iron deficiency in transfused and non transfused patients was 0% and (6/38) 15.8% respectively with an overall prevalence of 9% [9]. The prevalence of iron deficiency was higher in this study compared to that of the above countries. The reason for this cannot be readily explained as countries like Senegal, Brazil and Yemen are developing countries like Nigeria. In USA and probably in Jamaica, one may speculate that the children have better nutrition and probably a higher transfusion rate per individual although this was not so stated in any of the above studies.

As was seen in this study, interval of blood transfusion prior to the study period significantly affected the iron status as patients who had not been transfused for more than 5 years had significantly higher prevalence of iron deficiency compared to those who received

blood less than one year prior to the study. This further buttresses the fact that previous transfusion especially after a long interval is not protective against iron deficiency in SCD children. Iron overload was not seen in any of the subjects studied suggesting that the frequency of blood transfusion in these children was not high enough to predispose them to iron overload. Also, it suggests that the caregiver of these patients were not erroneously giving them blood tonic in an attempt to raise their PCV. This is reassuring as this practice would have been detrimental to the wellbeing of the patients. However, what appeared to be prevalent was iron deficiency in both the transfused and non transfused subjects.

CONCLUSION:

Although blood transfusion occurs commonly in SCD children, this practice is not protective against the occurrence of iron deficiency especially when the last blood transfusion is more than 5 years ago. Iron deficiency was highly prevalent among our SCD children studied.

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