ORIGINAL ARTICLE

Prevalence of hypoxemia among children with sickle cell anemia during steady state and crises: A cross-sectional study

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Abstract

Background: Patients with sickle cell anemia (SCA) are prone to recurrent pain crises related to red blood cell sickling and vaso-occlusion with subsequent tissue hypoxia. Alveolar hypoxia has been shown to be associated with entrapment of sickle cells in the pulmonary microcirculation which may propagate a cycle of further hypoxemia and sickling. Pulmonary complications are common in sickle cell disease (SCD) and may exacerbate microvascular occlusive phenomena. Thus, detecting hypoxemia is of particular importance in SCD.

Objectives: This study was designed to determine the prevalence of hypoxemia among children with SCA and compare the oxygen saturation of those in crises with those in steady state.

Materials and Methods: This is a prospective observational study involving 46 children with SCA in steady state, 42 with crises, and 42 with HbAA genotype carried out between August and December 2010. The study compared the oxygen saturation of sickle cell anaemic children in steady state and in crises with normal hemoglobin genotype using Nellcon pulse oximeter while the hemoglobin concentration was analyzed using automated Sysmex KX-21N model.

Results: A total of 130 participants aged 6 months to 18 years were recruited. The overall prevalence of hypoxemia in this study was 13.8%. Hypoxemia was highest among SCA patients in the crisis state (23.8%) compared to 13% and 0% for those in the steady state and in those with normal hemoglobin genotype, respectively ($\chi^2 = 6.425$, $P = 0.04$). Hypoxemia was higher among those with hemoglobin less than 5 g/dl (30%) and least among those whose hemoglobin levels were 10 g/dl and above.

Conclusions: Hypoxemia was significantly higher among children with SCA during Vaso-occlusion crises. We recommend that one should have a high index of suspicion and take prompt action in managing these individuals especially those with acute chest syndrome.

Key words: Enugu, hypoxemia, oxygen saturation, sickle cell anemia

Introduction

Sickle cell anemia (SCA) is a genetic hematological disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape.[1] This hereditary disorder contributes the equivalent of 3.4% mortality in children <5 years worldwide.[2] Sickle cell disorders were originally found in the tropics and subtropics but are now common worldwide due to migration of people from the tropical to temperate zone.[2] The prevalence of SCA in Nigeria ranges from 0.4% to 3%.[3] About 85% of sickle cell disorders and over 70% of all affected births occur in Africa.[4] It is worthnoting that at least 5.2% of the world population carry a significant trait.[5] Patients with this disease suffer from a variety of clinical events associated with small and large vessel occlusion, including vaso-occlusive painful episodes, strokes, and acute chest syndrome.[5] Nduka *et al.*[5]

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noted 25% of cases of vaso-occlusion among patients with SCA while Westerman and colleagues[6] observed pulmonary infarction in one out of every six patients with this disorder.

Sickle cell anemia patients with hypoxemia appear to have increased endothelial dysfunction, coagulation activation, and inflammation compared with patients without hypoxemia and this is worse in crises. The endothelial dysfunction, as well as coagulation activation, is due, at least in part, to hemolysis, with resultant scavenging of nitric oxide.[7]

The diseases associated with hemoglobin S (HbS) present a wide clinical spectrum with SCA being the most severe form. In SCA, the red blood cells undergoes deformation and assume a sickle shape under low oxygen tensions, which results in polymer formation.[1,5] The sickled red blood cells can then block small blood vessels, causing pain and impaired circulation, decrease the oxygen-carrying capacity of the red blood cell, and ultimately decrease the cell's lifespan.[5] A right-shifted oxyhemoglobin dissociation curve is found in SCD and has been thought to result in abnormally low arterial oxygen saturation (SO_2), even when oxygen partial pressure (PO_2) is normal.[8] Oxyhemoglobin dissociation curves measure the affinity for oxygen and its delivery to the tissues.[9] This means therefore that oxygen saturation in SCD could be lower than the normal.[9] Oxygen saturation is measured invasively by the arterial blood test but can also be measured noninvasively by pulse oximetry (SpO_2).[8,10] Pulse oximeters are particularly useful in rural communities of developing countries.[10] The use of clinical signs as alternative to pulse oximeters has limited application as no clinical signs have been shown to be a reliable predictor of hypoxemia.[11]

Normal blood oxygen readings using pulse oximeters range from 95 to 100% at the sea level.[12] There have been conflicting reports in the literature on the accuracy of pulse oximeter in predicting hypoxemia in SCD patients.[13] However, Pulse Oximetry and Transcrainal Doppler Ultrasonography show steady-state hemoglobin desaturation as a common finding in SCA. This hemoglobin desaturation predisposes to stroke by limiting oxygen delivery to the brain.[8,14] In this study, the oxygen saturation by pulse oximetry of SCA patients in steady and vaso-occlusive crisis states is compared with a control group of children with HbAA.

Many individuals with sickle cell disease (SCD) have arterial oxyhemoglobin desaturation during the steady-state in the absence of overt cardiopulmonary illness.[15] Steady-state desaturation in SCD is partly caused by a rightward shift of the oxyhemoglobin dissociation curve because of the properties of sickle hemoglobin (Hb S) in solution[16] and the effects of chronic anemia mediated through 2,3-bisphosphoglycerate.[17] The findings from this study may add to the increasing knowledge of this challenging disease and may help to improve management of children with this disorder since there has not been much study among children in this locality.

In addition, this study would also help in establishing baseline values of oxygen saturation indices among SCA patients in steady state.

Materials and Methods

Study area
The study was carried out at the children emergency room (CHER), children's outpatient (CHOP), and consultants' clinics of the Paediatrics Department of the University of Nigeria Teaching Hospital (UNTH) Ituku-Ozalla, Enugu, Nigeria.

Study population
The subjects were children with SCA in steady state aged 6 months to 18 years attending the sickle cell clinic. There are about 700 children registered at the sickle cell clinic of UNTH, Enugu, with an average of five new patients per month. The clinic runs on Mondays with a weekly attendance of between 15 and 20 patients. It is run by three consultants, two senior registrars, and four Registrars.

The control population were children who were apparently healthy with normal hemoglobin genotype (HbAA) confirmed by hemoglobin electrophoresis. UNTH has a total bed space of 480 and provides specialized services in the major fields of medicine. It is a referral centre for various health centers in the Enugu state and environs. The Paediatrics Department comprises the children's outpatient clinic (CHOP), the children emergency room (CHER), the general ward, and the new born special care unit (NBSCU). The childrens' outpatient clinic runs every weekday and a total of 840 patients are seen monthly.

Study design
This was a prospective cross-sectional study using a structured questionnaire. The questionnaire contained information on bio-data, clinical state of the client (steady state, crises, normal hemoglobin genotype), oxygen saturation and the hemoglobin level.

Participants
The participants comprised SCA patients aged 6 months to 18 years (46 in steady state and 42 in vaso-occlusive crisis). Another 42 non-SCA patients served as the control matched for age and sex. These were children who have been treated for acute uncomplicated malaria and attending the paediatric follow-up clinic. The participants were enrolled between August and December 2010.

Inclusion criteria
Patients with HbSS genotype, diagnosed by cellulose acetate electrophoresis at pH of 8.6:

(a) who were clinically stable for a minimum of 4 weeks

before recruitment for the "steady state" group.

(b) who were in any form of vaso-occlusive crises for the "crises" group.

Children attending the paediatric follow-up clinic who were treated for uncomplicated malaria served as control. Their HbAA genotype was confirmed by cellulose acetate electrophoresis at pH 8.6, and they were matched for age and sex with the SCA patients.

Exclusion criteria

Patients with history of blood transfusion within the preceding 3 months.

Materials and procedures

The questionnaire used for this study contained information on bio-data such as age and sex as well as clinical state (steady state, crises and hemoglobin genotype). The oxygen saturation was determined using a Nellcon non-invasive pocket pulse oximeter (A320 Shangai Ltd). The finger tip was used for this measurement, and this was done for about 2 min on two occasions and the average taken and documented. The same pulse oxymeter was used for all clients studied. It has an in-built sensor and does not require recalibration before use. Hypoxemia was defined as oxygen saturation of less than 90% in line with WHO recommendation.[15] The hemoglobin concentration was estimated using an automated Sysmex machine (KS21N model). Enrolment was within 24 h of admission into the emergency room for those in crises.

At the time of enrolment, the principal investigator measured the oxygen saturation and took sample for hemoglobin estimation and information obtained was entered into the questionnaire. He stays within working hours in the hospital and is called when there is emergency.

Data analysis

The data were analyzed using SPSS version 17. Descriptive statistics was used in reporting prevalence. χ^2-test was used for statistical significance of categorial variables. The level of statistical significance used was $P < 0.05$ and 95% confidence interval reported where necessary.

Consent and ethical approval

The participants were consecutively enrolled and consent was sought from their caregivers and the client in addition for the older children. Ethical approval was obtained from the Health Research and Ethics Committee of the University of Nigeria Teaching Hospital, Ituku-Ozalla.

Results

Demography of the participants

A total of 130 children aged 6 months to18 years were enrolled. The mean age (± 2 SD) was 8.4 ± 5.38 years. Forty-six of them

were in steady state, 42 had various forms of vaso-occlusive crises, and another 42 with normal hemoglobin genotype (HbAA). Eighty-two (76.3%) participants were males and 48 (23.1 %) were females. The age and sex distributions of the participants are shown in Table 1.

Hypoxemia among the various groups of patients

The overall prevalence of hypoxemia in this study was 13.8%. Hypoxemia was highest among the SCA patients in the crisis state (23.8%) compared to 13% and 0% for those in steady state and with normal hemoglobin genotype, respectively [Table 2]. This was statistically significant ($\chi^2 = 6.425$, $P = 0.04$). A sub-analysis however, of hypoxemia prevalence between the steady state and the normal hemoglobin groups only showed no statistically significant difference ($\chi^2 = 1.82$, $P = 0.17$).

Hypoxemia and oxygen saturation

Hypoxemia was higher among those with hemoglobin <5 g/dl (30%). This was followed by those with hemoglobin between 5 and <10 g/dl (18.5%) and least among those whose hemoglobin levels were 10 g/dl and above as shown in Table 3. This difference is statistically significant ($P = 0.014$).

Discussion

The findings in this study have demonstrated a significant difference in oxygen saturation values and hypoxemia among SCA children in vaso-occlusive crises on one hand compared to those in steady state and those with normal hemoglobin genotype on the other hand. The prevalence of hypoxemia among SCA children is 13%. This prevalence is attributable to the chronic anemic state, microvascular occlusion of the circulation by sickled hemoglobin and constant pertubation of the endothelial membrane and consequent elaboration of endothelial molecules which are commonly seen among SCA children especially those with various types of vaso-occlusive episodes.[7] Hypoxemia and lower oxygen saturation values were highest among sickle cell patients in crises, followed by those in steady state and none among individuals with normal hemoglobin genotype. Possible reason for this low oxygen saturation in crises could be due to microvascular occlusion of pulmonary vasculature, platelet scavenging and an increase in elaboration of nitric oxide.[12] Homi *et al.*[15] in Jamaica noted similar findings. They determined the oxygen saturation of children with homozygous sickle cell (SS), sickle cell hemoglobin C (SC), and normal hemoglobin (AA) and noted reduced values in children with SCA. It has also been noted that children with SCA usually have mild hypoxemia and their oxyhemoglobin dissociation curve is shifted to the right further explaining the lower oxygen saturation seen among them.[10]

Fawibe,[18] however, noted that hypoxemia could be due to intrapulmonary shunting, membrane diffusion defects, and

Table 1: Age and sex distribution of the study participants

Genotype	0.5–5 years		6–10 years		11–15 years		16–18 years	
	M	F	M	F	M	F	M	F
Steady state	9	3	10	4	13	5	1	1
Crises state	6	5	9	6	6	4	4	2
AA	12	11	5	4	5	2	2	1
Total	27	19	24	14	24	11	7	4

Table 2: Prevalence of hypoxemia among SS patients during crises and steady state compared to controls

Genotype	Hypoxemia		
	Absent (%)	Present (%)	Total N (%)
Steady state	40 (87)	6 (13)	46 (100)
Crises state	32 (76.2)	10 (23.8)	42 (100)
AA	42 (100)	0 (0)	42 (100)

$\chi^2=6.425$, df=2, $P=0.04$

Table 3: Relationship between hypoxemia and hemoglobin concentration of all the subjects and control

Hemoglobin conc. (g/dl)	Hypoxemia		
	Yes (%)	No (%)	Total
<5	3 (30)	7 (70)	10 (100)
5 to <10	15 (18.5)	66 (81.5)	81 (100)
10 and above	0 (0)	33 (100)	33 (100)

$\chi^2=8.58$, df=2, $P=0.014$

an eventual shift of the dissociation curve to the right. This could lead to restrictive impairment of ventilatory function. Furthermore, there is a positive correlation between hemoglobin correlation and oxygen saturation.

There were no statistically significant difference in the oxygen saturation values of the SCA patients in their steady state and those children with normal Hb genotype. The reason for this could be that while oxygen affinity is low under hypoxic conditions, it is normal at normal arterial pressure[8] and SCA children have arterial oxygen saturation close that with normal hemoglobin genotype. This is in keeping with the study of Abdu *et al.*[8] who retrospectively examined 50 blood gas samples from SCD patients and from controls matched for pH, and carboxyhemoglobin. Their control data fell close to the Severinghaus's curve, as did non-hypoxemic children with SCD.

Here, we demonstrated that males are more likely to have lower oxygen saturation than females, a finding not reported in past studies.[19] The effect of gender on oxygen saturation was small and probably not clinically significant, but the difference was statistically significant. The reason for this low oxygen saturation in males could be due to a transcription factor for hemoglobin F and Endothelial B receptor (ETBR)

which have been linked to X chromosome.[20] This receptor is important in the body's internal ability to control pain by releasing endorphins. Males have less receptor when compared to females. Females also have higher oxygen delivery to the tissues and hence vaso-occlusive destruction of tissues are usually minimal.[21]

Although the frequency of some complications of SCD may differ between sexes, we did not investigate any potential biological explanations for this interesting finding.

The use of pulse oximetry in developing countries instead of oxygen gas has been supported in various studies. Blaisdell *et al.*[22] noted that the mean difference between pulse oximetry and measured oxygen saturation was 5.0% and the precision was 5.3; 33% percent were predicted to be hypoxic by pulse oximetry with values <93% despite an arterial oxygen partial pressure greater than 70 mmHg.

Conclusions

There is a high rate of hypoxemia among SCA patients in stable state which is worse during crises compared to children with normal Hb genotype. Hypoxemia was significantly higher among children with SCA during vaso-occlusive crises. We recommend that one should have a high index of suspicion and take prompt action in managing these individuals with acute chest syndrome.

Acknowledgments

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