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A Comparative Study of Haematological Parameters between Sickle Cell Anemia Patients on Hydroxyurea and Hydroxyurea Naïve Patients

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Abstract
Sickle cell anemia is a genetic blood disorder that requires the patients to take a lifelong regimen of hydroxyurea drugs. Kenya, being a third world country, many of these patients are not able to afford to sustain their supply of the drug hence are off it most of the time. The primary aim of this study was to determine whether there were haematological differences between the sickle cell patients taking hydroxyurea and hydroxyurea naïve patients. After obtaining consent and assent, a 2ml blood sample was collected from each study participant. A full blood count was run on the SYSMEX XT – 2000i and data entered into an Excel sheet. The parameters of interest were the hemoglobin, white blood cell count, and platelet count. A questionnaire was used to collect sociodemographic information and clinical history information. Ninety two sickle cell anemia patients participated in this study. Of these 46 were on hydroxyurea while the other 46 were off hydroxyurea. The mean Hb of those on hydroxyurea and those not on hydroxyurea was10.4 and 9.0 respectively (P value = 0.01). The mean WBC of those on hydroxyurea and those not on hydroxyurea was 11.0 and 14.7 respectively (P value =0.005). The mean Plt of those on hydroxyurea and those not on hydroxyurea was 384 and 485 respectively (P value= 0.01). A clinically significant difference between the Hb, WBC and platelet counts was noted between the 2 groups thus suggesting a positive impact of Hu on the haematological parameters of sickle cell patients. Studies such as this could help policy makers in devising strategies to make hydroxyurea more affordable to the Kenyan sickle cell population.

Background
Sickle cell anaemia (SCA) is an inherited blood disorder that has a proven a major health challenge in Kenya as well as other parts of the world[1,2,3]. It is an inherited genetic disorder that affects the haemoglobin molecule found in the red blood cells[4,5,6]. It is not a contagious condition and

thus not transmissible from one individual to another. Haemoglobin is the protein structure responsible for transporting oxygen and carbon dioxide molecules within the blood[7,8,9]. An individual inherits two haemoglobin genes, one from each parent[4,5]. When only one of these is a haemoglobin S gene, it results in the individual

being a carrier, whereas if both the haemoglobin genes inherited by the individual are of haemoglobin S genotype, it results in sickle cell anemia[4,5,7]. Thus sickle cell anaemia is said to be a recessive disorder[4]. People who are carriers of HbS are said to have sickle cell trait and do not exhibit any symptoms of sickle cell. They lead fairly normal lives. Persons with sickle cell anaemia, however, exhibit various symptoms as a result of the condition, that affect their ever day lives[4,9].

A point mutation within the DNA sequence is the primary cause of sickle cell anaemia[8]. This mutation occurs in Beta- globin gene that is located on chromosome 11 where an Adenine (A) is replaced by a Thymine (T)[2,5,9,11]. This leads to an alteration of the amino acid where the glutamic acid is replaced by valine[2,5,6,9]. This change causes the body to produce HbS instead of the normal HbA[5,6,10.] The resultant red blood cells possess the tendency to sickle in hypoxic conditions leading to a crescent shape and leading to various complications[1,6,11]. Normal red blood cells are disk shaped and flexible. However, sickle cell red blood cells are sickle shaped and rigid[7,9] They do not survive as long as normal red blood cells do. This causes them to have difficulty passing through blood vessels and stick to the walls of these [7,10]. This hinders the flow of blood to various tissues and thus oxygen cannot reach these sites[7]. This in turn leads to pain which is referred to as vaso occlusive crises[12]. The sickle cells do not last as long as normal red blood cells[12,13.] Normal red blood cells can last for about 90 to 120 days in circulation whereas sickle cells may last only up to 10 to 20 days[7,16]. Under normal circumstances, the body keeps on producing red blood cells to replace the old ones once they get destroyed but in sickle cell anaemia, the bone marrow has a hard time keeping up with the rapid rate of destruction leading to anaemia[17]. Other symptoms include high risk of serious infection, shortness of breath, acute chest syndrome, delayed growth and stroke.

Hydroxyurea is currently one of the widely used drug available for the management of sickle cell anaemia[3]. It works by increasing the synthesis of HbF by the body[5,12]. It also serves an inhibitory role on the polymerization of the sickle cells[12,16]. The main aim in management of sickle cell patients is to achievement of steady state. Steady state is the situation whereby the patient is not undergoing hemolytic crisis, is not experiencing pain and does not depict any clinical illness for a period preceding 3 months[19]. A sickle cell patient is said to be in steady state when they have not had an acute pain episode, a blood transfusion or any illness for a continuous 3 months[20]. The use of hydroxyurea has been found to lead to an overall improvement in the quality of life for sickle cell patients by having a reduction in the number of hospitalizations, painful crises and episodes of acute chest syndrome suffered by the patients[6,8,12]. However, despite these positive effects depicted by the drug, HU continues to be highly underutilized[13]. One of the reasons for this is the failure to maintain compliance by the patients or their relatives as well as inexperience among healthcare givers[17]. The limited availability of HU also contributes to this non compliance as most patients are not able to afford the drug. In Kenya, HU has not been incorporation in the Kenya National Guidelines for use in children of under the age of 5years[2,12, 13,15]. Understanding the haematological profiles of sickle cell patients in steady state can be a predictor of clinical outcome and help in devising management strategies for the patients. In light of this, it is important to know whether there is any clinically significant difference between the full blood counts of those steady state sickle cell patients taking hydroxyurea and those not taking hydroxyurea.

Methods
Study site and population
This cross – sectional study was carried out at the Kenyatta National Hospital from August 2018 to January 2019. The study population was

comprised of sickle cell anemia patients attending the hospital's hematology clinic. A total of forty six steady state sickle cell anemia patients taking hydroxyurea for at least 3 months were recruited as well as forty six steady state sickle cell anaemia patients who had not taken hydroxyurea in at least 3 months, were recruited into the study. Steady state was defined as having not had an acute pain episode, a blood transfusion or any illness for the last previous 3months. The patient's steady state was confirmed through their clinical notes. Patients diagnosed with acute renal disease were excluded from the study.

Sample collection and analysis

Interviewer administered questionnaires were used to obtain relevant information on socio-demographic and clinical history of the participants. Informed consent was obtained from all participants above 18years of age and assent gotten from the parents/guardians of the participants below 18 years of age. Two millilitres of venous blood were collected into ethylene diamine tetraacetic (EDTA) vacutainers for a full blood count. These were run on the SYSMEX XT – 2000i blood count machine and data on the Hb, WBC and platelet count gotten for each sample.

Statistical analysis

The Hb, WBC and platelet count data was the entered into Microsoft Excel, cleaned and validated. A two tailed t-test was used to compare the means of the Hb, WBC and Platelets between the 2 samples. A confidence interval of 95% was set at a *P*- values less than or equal to 0.05.

Ethical consideration

Ethical approval was obtained from the Kenyatta National Hospital – University of Nairobi Ethical Research Committee in accordance with the code of ethics for biomedical research involving human subjects (reference No. P 289/04/2018). Written informed consent and assent was obtained from all participants.

Results

A total of 92 subjects participated in the study. These included 46 patients on hydroxyurea and 46 hydroxyurea naïve patients. The mean Hb of those on hydroxyurea was 10.4g/dl while that of those not on hydroxyurea was 9.0g/dl (Table1 and the p value = 0.01). The mean WBC of those on hydroxyurea was 11.0 x10^3/uL while that of those not on hydroxyurea was 14.7 x10^3/uL (Table2, the P value =0.005). The mean Plt of those on hydroxyurea was 384.6 while that of those not on hydroxyurea was 485.5 (Table3, the P value= 0.01).

Table 1: t-Test: Two-Sample Assuming Unequal Variances for Hb levels

	HB	*HB-2*
Mean	10.44434783	9.060434783
Variance	7.044567343	5.944062029
Observations	46	46
Hypothesized Mean Difference	0	
P(T<=t) two-tail	0.010784954	

Table 2: t-Test: Two-Sample Assuming Unequal Variances for WBC count

	WBC	*WBC-2*
Mean	11.00434783	14.78478261
Variance	22.38931401	58.99509662
Observations	46	46
Hypothesized Mean Difference	0	
P(T<=t) two-tail	0.005768337	

Table 3: t-Test: Two-Sample Assuming Unequal Variances for platelet count

	PLT	*PLT-2*
Mean	384.6956522	485.5869565
Variance	28032.3942	39524.60338
Observations	46	46
Hypothesized Mean Difference	0	
P(T<=t) two-tail	0.010023191	

These results correspond with studies carried out in the USA where the WBC and platelet counts were found to decrease while the Hb levels increased in sickle cell anemia patients taking hydroxyurea compared to those who took a placebo drug[12]. Another study also showed

significant difference between the parameters with Hb levels rising from 8.3 g/dl before Hu to 9.0 g/dl after Hu,(P = 0.0003), reductions in the numbers of leukocytes from 10.0x10^3/uL before Hu to 5.7x10^3/uL after Hu (P < 0.0001) and platelet count reduction from 459 x10^3/uL to 373 x10^3/uL (P = 0.0002)[22].

Discussion

This study showed that there was a significant difference the Hb, WBC and platelet values between steady state sickle cell anaemia patients on Hu and steady state sickle cell anaemia patients not on Hu. The Hb was seen to be higher in patients taking Hu while the WBC and platelet counts were lower. The higher Hb values in those taking Hu is attributed to the action of Hu increasing HbF. The lower WBC nad platelet counts could be attributed to the cytoreductive action of the drug

Despite the documented evidence of the benefit of Hu to sickle cell patients, it is still widely underused. We hope this study together with others published in recent times, will continue to encourage physicians to emphasize on the need for sickle cell patients to use hydroxyurea.

Conclusion

The patients on hydroxyurea presented better values for their hemoglobin, white blood cell and platelet counts. Based on this, the authors suggest that policy makers and health providers improve health education among sickle cell patients on the importance of hydroxyurea and also make these drugs more affordable to all sickle cell patients.

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