ISSN: 2279 - 0594

Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
Volume 4, Issue 3, May-June, 2015, 11-14

Research Article

HAEMOGLOBIN F LEVEL AND HAEMATOLOGICAL FEATURE AMONG SUDANESE CHILDREN WITH SICKLE CELL ANAEMIA UNDERGOING HYDROXYUREA THERAPY

[1]Fatima A. A. Ahmed and [2*] Mahdi H. A. Abdalla

[1]Faculty of Medical Laboratory Sciences, Alneelain University, Sudan

[2]Department of Haematology, Faculty of Medical Laboratory Sciences, Omdurman Ahlia University, Sudan

Received 30 April 2015; Accepted 15 May 2015

ABSTRACT

Sickle cell anemia (SCA) is one of the major types of anemia found in Sudan.The aim of this study is to evaluate the effect of Hydroxyurea (HU) treatment on Hb F level, reticulocyte count and the haematological feature among Sudanese children with SCA. The study included 38 children with SCA who were started a HU treatment(20mg/kg two times per week) following enrollment in the study. 2ml EDTA blood samples were collected from each patient at 4 time points (at the baseline, one month, two months and three months of HU treatment) for complete blood count (CBC), reticulocyte count and Hb F estimation.Our study revealed that haematological values, reticulocyte count and Hb F levelwere significantly improved after 3 months of HU treatment,this improvement was observed from the first month of HU treatment with further improvement in the second and third months. the rise in Hb F level is probably not the only mechanism of beneficial effect of HU. Other mechanisms are likely to contribute to the clinical benefits of HU.Our study revealed no significant correlation between Hb F level and the improvement in the heamtlogical parameters;this finding may suggest that, the rise in Hb F level is probably not the only mechanism of beneficial effect of HU. Other mechanisms are likely to contribute to the clinical benefits of HU.

Keywords: SCA, Hydroxyurea, Haemoglobin F, Reticulocyte count, Sudan.

INTRODUCTION:

A point mutation in the sixth position of the ß-globin polypeptide chain in chromosome 11 leads to the substitution of valine for glutamic acid, thereby forming hemoglobin S (Hb S) and determine the sickle cell disease (SCD)(1,2). Hb S, in low oxygen tension, undergoes a change in its molecular conformation triggering the formation of polymers that transform the classical shape of red blood cells to a new cellular structure assuming sickle shape (3). The homozygosity of sickle cell genes (HbSS) results in sickle cell anemia (SCA), while the heterozygosity results in other sickle cell diseases (SCD) which include sickle cell trait with one sickle cell gene and a normal haemoglobin gene (HbAS), and a double heterozygosity of a sickle cell gene with other abnormal haemoglobin variants gene (e.g. HbSC) (4). SCA is characterized by chronic intravascular and extravascular haemolysis. Sickling- induced membrane fragmentation and complement-mediated lysis causing intravascular destruction of red cells. Membrane damage also leads to extravascular haemolysis through entrapment of poorly deformable cells in the spleen and removal of these cells by macrophages (5).Pathophysiological studies have shown that the dense, dehydrated red cells play a central role in acute and chronic clinical manifestations of SCA, in which intravascular sickling in capillaries and small vessels leads to vaso-occlusion and impaired blood flow (6,7). HbF is the most powerful modulator of the clinical and hematologic features of sickle cell anemia (8,9). Higher HbF levels were associated with a reduced rate of many clinical complications in SCA (10). Many epidemiologic studies suggested that disease complications most closely linked to sickle vaso-occlusion and blood viscosity were robustly related to HbF concentration, whereas complications associated with the intensity of hemolysis were less affected (11). Hydroxyurea (HU), an antineoplastic drug, increases the production of fetal hemoglobin (12,13). There is an evidence that the beneficial effect of HU is not only limited to inducing increases in Hb F, as many patients demonstrate clinical improvement before any significant increase in Hb F appears (14,15).HUhas been shown to reduce pain crises and lessen the anemia, acts as anti-inflammatory agents by inhibiting the production of white cells, increases the MCV, and a potent vasodilator and inhibitor of platelet aggregation (16). The aim of this study is to evaluate the effect of HU treatment on Hb F level and the

*Corresponding author: Mahdi H. A. Abdalla | E-mail: mahdi_razig@hotmail.com

haematological feature among Sudanese children with SCA.

MATERIALS AND METHODS:

This is a prospective cross-sectional study included 38 children withSCAwhohave attended, or hospitalized in, Gaffer Ibn Auf hospital in Khartoum state, Sudan;patients were started a HU treatment(20mg/kg two time per week)following enrollment in the study. 2ml EDTA blood samples were collected from each patient at 4 time points (at the baseline, one month, two months and three months of HU treatment)for complete blood count (CBC), reticulocyte count and Hb F estimation.Laboratory analyses wereperformed at the Department of Hematology, Faculty of Medical Laboratory Sciences, Alneelain University, Sudan.CBC was performed by (Sysmex KX-21N). Reticulocyte count wasperformed on a thin blood film using a supravital stain.Hb Fwas measured by quantitative electrophore-sis.

Statistical analysis was performed usingstatistical package for social science (SPSS) software. Descriptive analysis was used to evaluate patient's data.A repeated measures ANOVAwas performed to study the effect of HU treatment on the haematological parameters in each time point. P value < 0.05 wasconsidered statisti-cally significant.

RESULTS:

The study included 28(74%) maleand 10 (26%) female; their median age was 7.5 years, with minimum age of 2 year and maximum of 16 years. All patients were tested for the blood cell count, reticulocyte count and Hb Flevel. At base line of HU treatment:78 % of patients were hospitalized for painful crises; 79% were severely anaemic with maximum Hb level 7.0 gm/dl; 90 % were presented with leukocytosis, with TWBC count greater than $11X10^9$/l; and 40 % have thrombocytosis with platelets count greater than $450X10^9$/l.

A repeated measures ANOVA with a Greenhouse-Geisser correction determined that haematological values, reticulocyte count and Hb F level were significantly differed between time points with the following results: mean Hb level ($F(1.950, 72.151) = 118.705$, P 0.000); mean TWBC count ($F(1.957, 72.397) = 27.694$, P 0.000); mean platelets count ($F(1.815, 67.168) = 43.839$, P 0.000); mean reticulocyte count ($F(2.216, 81.986) = 115.563$, P 0.000); and mean HbF level ($F(1.340, 49.575) = 208.824$, P 0.000).Post hoc tests using the Bonferroni correction revealed that haematological values, reticulocyte count and Hb F levels were significantly improved from pre-treatment point to one month point of treatment, from one month to 2 months point of treatment and from 2 months to 3 months point of treatment (Table 1). Painful event was observed in 37% of patient after 3 months of HU treatment. No correlation was observed between Hb level (P value 0.829), WBC count (P value 0.444), platelet count (P value 0.148) and reticulocytes count (P value 0.796), and Hb F at 3 months of HU treatment.

Table 1 Results of the haematological values, reticulocyte count and Hb F between different time points.

Parameter	Base line vs one month of treatment	One month vs 2 months of treatment	2 months vs 3 months of treatment
Hb mean±SD (g/l)	5.9 ± 1.7 vs 6.7 ±1.5 (p 0.000)	6.7 ±1.5 vs 7.7 ±1.5 (p 0.000)	7.7 ±1.5 vs 8.7 ±1.4 (p 0.000)
TWBC mean±SD (X109/L)	19.7 ±8.9 vs 16.3 ±7.1 (p 0.001)	16.3 ±7.1 vs 14.0± 6.0 (p 0.050)	14.0 ± 6.0 vs10.9 ±5.2 (p 0.001)
Platelets mean±SD (X109/L)	463±199 vs 366 ± 152 (p 0.000)	366±152 vs 316 ±127 (p 0.019)	316 ±127 vs 243± 98 (p 0.000)
Reticulocyte count (%)	14.7±5.0 vs 11.7 ± 4.6 (p 0.000)	11.7 ± 4.6 vs 8.5 ± 3.0 (p 0.000)	8.5 ± 3.0 vs 6.6 ±3.0 (p 0.000)
Hb F mean±SD (%)	5.1 ± 3.7 vs 9.0 ±4.3 (p 0.000)	9.0 ±4.3 vs 13.7±5.5 (p 0.000)	13.7±5.5 vs 17.8 ± 6.9 (p 0.000)

DISCUSSION:

Our study evaluated the effect ofHydroxyureaon the haematological values including Hb level, WBC count, Platelet count, Reticulocytes count and Hb Flevelamong 38 sickle cell children inadministration of 3 months' HUtreatment.HU had been approved by theUnited America Food and Drug Administration (FDA) for use in patients whosuffer fromSCAand severe painful crisis.Our study showed a significant increase in Hb F level after 3 months of HU treatment, with astatistically significant increase in Hb F level from the base line treatment to one month of treatment, with further increase from the first month to second month and from the second month to the third month of treatment, this finding supporting the results of other studies (17,18).

Our study revealed that haematological values (Hb level, WBC count, and Platelet count) were significantly improved after 3 months of HU treatment, this improvement was observed from the first month of HU treatment with further improvement in the second and third months. Reticulocyte count was also significantly reduced after the 3 months of HU treatment, with a reduction observed from the first month, with further reduction in the second and third month.Similar finding were reported in previous studies (19, 20).Borbaet al suggested that vaso-occlusion is initiated by reticulocytes that temporarily seize deoxygenated mature red blood cells. WBC counts have been considered a risk factor in the development of pain and infarctions (18). Our results supported these findings, since the WBC and reticulocyte counts were higher in the pre-treatment point than after 3 months of treatments, with a significant reduction in the painful event frequency among the study group.

It has been well established that high level of HbF reduces the severity of SCD by preventingthe formation of hemoglobin S polymers. Our study revealed no significant correlation between Hb F level and the improvement in the heamtlogical parameters,this finding may suggest that, the rise in HbF level is probably not the only mechanism of beneficial effect of HU. Other mechanisms are likely to contribute to the clinical benefits of HU.

In conclusion, our study evaluated the effect of Hydroxy urea on the haematological values, Reticulocytes count and Hb F level among 38 sickle cell children in administration of 3 months' HU treatment. Our study revealed that haematological values, reticulocyte count and Hb F levelwere significantly improved after 3 months of HU treatment, no significant correlation was observed between Hb F level and the improvement in the heamtlogical parameters.

REFERENCES:

1. Shiu Y, Udden MM, Mclntire LV. Perfusion with sickle erytrocytesup-regulates ICAM-1 and VCAM-1 gene expression in cultured human endothelial cells. Blood. 2000;95:3232-41.
2. Rosse WF, Narla M, Petz LD, Steinberg MH. New views of sicklecell disease, pathophysiology and treatment. Hematology Am SocHematolEduc Program. 2000:2-17.
3. Costa FF. Anemia Falciforme. In: Zago MA, Falcão RP, PaquiniR.Hematologia, Fundamentos e prática. São Paulo: Atheneu. 2004; 289-308.
4. Setty BN, Rao AK, and Stuart MJ. Thrombophilia in sickle cell disease: the red cell connection Blood. 2001; 98: 3228-3233
5. A Victor Hoffbrand. Daniel Catovsky. Edward GD Tuddenham. Anthony R Green. Postgraduate Haematology. Sixth edition; 2010.
6. Nitin J. A Review of Clinical Profile in Sickle Cell Traits. Oman. Med. J;2010 25: 3-8.
7. Nduka N, Owhochuku SM, Odike P. Current observations on sickle cell genotype in Nigeria. East Afr Med J .1993;70:646-9.
8. Powars D, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? Blood. 1984;63 (4) :921–926.
9. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639–1644.
10. Steinberg MH, Forget BG, Higgs DR, Weatherall DJ, editors. Disorders of Hemoglobin: Genetics, Pathophysiology, Clinical Management Cambridge, United Kingdom: Cambridge University Press; 7nd Ed2009.
11. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev. 2007;21(1):37–47.
12. Rodgers GP, Dover GJ, Noguchi CT, Schechter AN, NienhuisAW. Hematologic responses of patients with sickle cell disease to treatment with hydroxyurea. N Engl J Med. 1990;322:1037-45.
13. Charache S, Terrin ML, Moore MD, Dover GJ, Barton FB, EckertSV, et al. Effects of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med. 1995;332:1317-22
14. Huang J, Kim-Shapiro DB, King SB. Catalase-mediated nitricoxide formation from hydroxyurea. J Med Chem. 2004;47: 3495-501.
15. Halsey C, Roberts IA. The role of hydroxyurea in sickle celldisease. Br J Haematol. 2003;120:177-86.

16. Robbin B.P (edit by), Vinaykummel, ramzi S, cot ran, basic pathology.7thEd ;2003.

17. Bandeira FM, Peres JC, Carvalho EJ, Bezerra I, Araújo AS, Mello MR, et al. Hidroxiuréiaempacientes com síndromesfalciformesacompanhados no Hospital Hemope, Recife-PE.Rev Bras HematolHemoter. 2004;26: 189-94.

18. Borba R, Lima CS, Grotto HZ. Reticulocyte parameters and hemoglobin F production in sickle cell disease patients undergoing hydroxyl urea therapy. JClin Lab Anal. 2003;17: 66-72

19. Zakaria Mohammed Al Hawsawi CABP , Waheed Ahmed Turkistani CSBP ; Journal of Taibah University Medical Sciences 2008; 3: 129 – 134.

20. Santos FK and Caroline Nogueira Maia CN. Patients with sickle cell disease taking hydroxyurea in the Hemocentro Regional de Montes Claros. Rev Bras HematolHemoter. 2011;33:105-109.