**Article Original**

**Clinical and Biological Profile of Patients on Hydroxyurea at Mother and Child Center of Chantal Biya’s Foundation**

***Profil clinique et biologique des enfants drépanocytaires sous hydroxyurée au Centre Mère et Enfant de la Fondation Chantal Biya Yaoundé-Cameroun***

Anastasie Nicole Alima Yanda 1,2, Suzanne Sap Ngo-Um 1,3, Ousmane Itawa Hassanatou 3, Jobert

Richie Nansseu 4, Sandra Ayuk Tatah 3, Judith Marlyse Seungue 1, Estelle Wete 1, Paul Olivier Koki 1,3

|  |  |
| --- | --- |
|  |  |
| 1 Mother and Child Centre of the Chantal Biya Foundation, Yaounde, Cameroon2 School of Medicine, Higher Institute of Medical Technologies, Yaounde, Cameroon3 Department of Pediatrics and Pediatric Specialties, Faculty of Medicine and BiomedicalSciences of the University of Yaounde I, Yaounde, Cameroon4 Department of Disease, Epidemics and Pandemics Control, Ministry of Public Health, Yaounde,Cameroon**Corresponding author** : Suzanne Sap Ngo Um**Tél**:+237 677594797Mail : suzysap@gmail.com P.O Box : 9183, Yaounde**Keywords**: Sickle cell disease, hydroxyurea, Cameroon**Mots-clés** : Drépanocytose, hydroxyurée, Cameroun | **ABSTRACT** |
| **Introduction.** In Cameroon, sickle cell disease (SCD) remains a concerning condition, with a high proportion of severe forms that require intensification of treatment. Unfortunately, exchange transfusion is not practiced to date and hydroxyurea (HU) remains sparsely prescribed. There are very few studies evaluating the efficacy of HU in our context. We therefore undertook the present study to evaluate efficacy of HU on the clinical and biological profile of SCD children in Yaounde, Cameroon. **Patients and methods.** We did a retrospective cohort study including all sickle cell children aged 2 to 20 years, regularly followed-up at our center, and placed on HU for at least one year before the start of the study. We analyzed clinical data (transfusion needs, frequency of vaso occlusive crisis, serious complications), hemolysis and medullary activity indicators and hemoglobin level before and after initiation of HU with a 12 months follow up. Adverse effects were noted. **Results.** We included 30 patients with homozygous SCD from which 56.7% male. The median age was 96 months (IQR 72-142.5). The main indication of HU was a low basal hemoglobin level (46.7%), followed by severe vaso-occlusive crises leading to at least three hospitalizations per year (40.0%). At 12 months, we noticed a reduction of 90% of admissions and a reduction of duration of hospitalization. Significant increase of weight gain (p&lt; 0.001) and improvement of hemoglobin level. (p&lt;0.001). Few mild adverse effects were reported. **Conclusion.** Hydroxyurea improves clinical and hematological parameters of children and adolescents in MCC/CBF at 12 months. |
|  | **RÉSUMÉ** |
| **Introduction**. Au Cameroun, la drépanocytose demeure un problème de santé publique avec une grande proportion de formes sévères nécessitant un traitement intensif. Malheureusement l’échange transfusionnel n’est pas encore pratiqué et l’hydroxyurée (HU) est peu prescrit. Peu d’études ont évalué l’efficacité de ce dernier dans notre contexte. Ceci justifie le présent travail dont le but était d’évaluer l’efficacité clinique et biologique de l’HU chez des enfants drépanocytaires à Yaoundé, Cameroun. **Patients et méthodes** Nous avons réalisé une étude de cohorte rétrospective incluant des drépanocytaires âgés de 2 à 20 ans, sous HU depuis au moins 12 mois consécutifs, suivis dans notre centre. Nous avons analysé leurs données cliniques de sévérité de la maladie, les indicateurs d’hémolyse et d’activité médullaire et le taux d’hémoglobine à l’initiation de l’HU et à 12 mois de suivi. Les effets secondaires étaient notés. **Résultats.** Nous avons inclus 30 patients drépanocytaires homozygotes dont 56,7% était des garçons. L’âge médian était de 96 mois (EIQ 72-142,5). Les principales indications de mise sous HU étaient le taux d’hémoglobine bas (46,7%) et les crises vaso occlusives sévères (40%) entrainant au moins 3 hospitalisations annuelles. Après 12 mois, nous avons noté une réduction de 90% des hospitalisations ainsi que la durée d’hospitalisation. Nous avions une prise de poids significative (p&lt; 0.001) ainsi que l’augmentation du taux d’hémoglobine (p&lt; 0.001). Quelques effets secondaires mineurs ont été rapportés. **Conclusion.** L’hydroxyurée améliore les paramètres cliniques et biologiques des enfants et adolescents drépanocytaires au centre mère enfant de la Fondation Chantal Biya. |

**INTRODUCTION**

Sickle cell disease (SCD), also known as hemoglobin S disease, is an inherited autosomal recessive disorder occurring on chromosome 11. It is the most common genetic disease in the world with a clear predominance in the black population [1, 2]. In Cameroon, it constitutes a challenging public health problem two recent studies of neonatal screening showed 15% of carrier(sickle trait), 7,5‰ of sickle cell disease while a real prevalence of the disease in the country is unknown [3,4]. This disease is accompanied by numerous acute and chronic complications that cause high morbidity and mortality [1, 5, 6].

In northern countries, the quality and life expectancy of SCD patients has improved significantly in recent years thanks to neonatal screening, penicillin antibiotic prophylaxis, research and early detection of chronic complications, intensified treatment of severe forms by exchange transfusions and use of hydroxyurea (HU) [7,8,9].

In southern countries and Cameroon in particular, sickle cell disease remains a very concerning condition, with a high proportion of severe forms that require intensification of treatment [10, 11, 12]. Unfortunately, exchange transfusion is still not practiced to date (high cost, inadequate transfusion safety) and hydroxyurea remains sparsely prescribed (high cost, unavailable medication, reluctance of health care staff and patients, fear of undesirable effects including infertility).

There are very few studies dedicated to evaluating the efficacy of hydroxyurea in the management of severe sickle cell disease in Cameroon. In addition, and for a few years, SCD children followed-up at the Chantal Biya Foundation's Mother and Child Center (Yaounde, Cameroon) are treated with hydroxyurea when there are indications. We therefore undertook the present study to evaluate the effect of hydroxyurea on the clinical and biological profile of SCD children in Yaounde, Cameroon.

**MATERIAL AND METHODS**

**Design and location of the study**

We conducted a retrospective cohort study from August 1st, 2014 to July 31, 2015 in the Sickle Cell Child Care Unit of the Mother and Child Center /Chantal Biya Foundation (MCC /CBF). Located in the city of Yaounde, capital of Cameroon, this center has been thoroughly described elsewhere.

**Participants**

We included all sickle cell children aged 2 to 20 years, regularly followed-up at our center, and placed on HU for at least one year before the start of the study. We excluded children with sickle cell disease who had any other chronic condition (HIV immunodepression, tuberculosis), patients whose clinical records were unusable (incomplete biological data) and those whose treatment with HU was interrupted for at least 4 consecutive weeks during the study period.

**Data Collection**

We used a standardized questionnaire to collect sociodemographic data, co-morbidity factors, clinical and biological data before and after HU initiation as well as adverse effects. The data was collected at the time of initiation of HU then at 3, 6 and 12 months later, except for hemoglobin electrophoresis that was measured at initiation of HU and 12 months later. Clinical data included transfusion needs, hospitalizations, frequency and severity of vaso-occlusive crises and the occurrence of serious complications (acute chest syndrome, priapism, neurological incidents, etc.). As for the biological data, we noted the basic hemoglobin level (before initiation of HU), the hemolysis indicators (free bilirubin, lactate dehydrogenase (LDH) and medullary activity (reticulocyte, platelet, white blood cell levels)) and hemoglobin electrophoresis. The adverse effects sought were: headache, nausea, vomiting, as well as dermatological abnormalities (pruritus, appearance of the skin and nails).

**Statistical analysis**

The data was entered and coded using Microsoft Excel v 2010; we analyzed the data using SPSS v. 20.0 (IBM SPSS Inc., Chicago, Illinois, USA). The results are presented as numbers (percentages) for the qualitative variables and means ± standard deviation or medians (interquartile range) for the quantitative variables. Quantitative variables were compared using the Wilcoxon test or the Friedman test; the results were considered statistically significant for a value of p <0.05.

**Ethical considerations**

Our study was approved by the Institutional Committee of Ethics and Research of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I. We also obtained a research authorization from the MCC/CBF Directorate. Since the study was retrospective, patient consent could not be obtained. The anonymity of the patients and the confidentiality of the information collected were scrupulously respected.

**RESULTS**

Thirty patients (56.7% male) were included in this study. The ages ranged from 33 to 240 months with a median of 96 months (IQR 72-142.5). The most represented age group was 5-10 years old (56.7%, Table I). All patients had severe SCD diagnosed between 7 and 84 months of age with a median of 24 months (IQR 12-39).

|  |
| --- |
| Table I : Indications for hydrourea initiation  |
| Characteristic |  | Number (N = 30) | Percentage (%) |
| Age (years) | < 5 | 3 | 10.0 |
|  | 5-10 | 17 | 56.7 |
|  | 11-15 | 7 | 23.3 |
|  | 16-20 | 3 | 10.0 |
| Sex | Males | 17 | 56.7 |
| Indication for HU initiation |  |  |  |
|  | Prolonged VOC > 1 week/month without hospitalization | 6 | 20.0 |
|  | VOC with ≥ 3 hospitalizations/year | 12 | 40.0 |
|  | Severe acute chest syndrome | 3 | 10.0 |
|  | Neurological incident | 5 | 16.7 |
|  | Priapism | 2 | 6.7 |
|  | Elevated transfusion needs  | 10 | 33.3 |
|  | Basal Hb level <7g/dl | 14 | 46.7 |

HU: hydroxyurea; VOC: vaso-occlusive crisis

**Clinical and biological profiles before hydroxyurea initiation**

Table I depicts the various indications for HU initiation; one patient could present more than one indication. The main indication was a low basal hemoglobin level (46.7%), followed by severe vaso-occlusive crises causing at least 3 hospitalizations per year (40.0%) and an elevated transfusion need (33.3%; Table I). All patients were taking folic acid and 27 of them (90%) were on preventive antibiotherapy. Levels of hemoglobin, HbF phenotype and serum LDH before initiation of HU are presented in Table II, with respective medians of 6.7 g/l (6.0-7.5), 12.1% (IQR 7.2-18.2), and 2031 IU/l (1408-3560).

**Evolution of clinical and biological parameters from HU initiation until 12 months later**

Table II presents the evolution of various parameters between HU initiation and 3, 6 and 12 months later. After the first three months, one case (3.3%) of vaso-occlusive crisis causing a hospitalization was recorded; three patients (10%) were hospitalized, all of whom were transfused; one case of acute chest syndrome (3.3%) was reported but no case of priapism or neurologic incident occurred. During the second trimester, 6 patients (20%) were hospitalized and seven patients (23.3%) were transfused; one neurologic incident (3.3%) occurred, but no case of acute chest syndrome or priapism was recorded. During the second semester, 3 patients (10%) were hospitalized with a duration of hospital stay seeming to have decreased in comparison to that at HU initiation (median 7 vs 2 days); no case of acute chest syndrome, priapism or neurologic incident occurred.

Patients' weight gain improved from study baseline to endpoint (median 22 vs 24 kg, p <0.001). Likewise, the HbF percentage increased significantly, as well as the hemoglobin level and the mean corpuscular volume (all p values <0.001; Table II). By contrast but interestingly, the number of reticulocytes, white blood cells, platelets, and serum LDH titers significantly increased over time (p values <0.05; Table II).

|  |
| --- |
| Table II: Evolution of clinical and biological parameters  |
| Characteristic  | Before or at initiation of HU | At 3 months | At 6 months | At 12 months | p value |
| Patients with VOC causing hospitalization | 14 (46.7) | 1 (3.3) | 3 (10.0) | 0 (0.0) | / |
| Patients with prolonged VOC without hospitalization | 6 (20.0) | 1 (3.3) | 1 (3.3) | 1 (3.3) | / |
| Patients hospitalized  | 30 (100.0) | 3 (10.0) | 6 (20.0) | 3 (10.0) | / |
| Days of hospitalization/month? | 7 (6.5-10) | 3 (2-/) | 6 (3.8-7.8) | 2 (2-/) | / |
| Patients transfused  | 16 (53.3) | 3 (10.0) | 7 (23.3) | 1 (3.3) | / |
| Number of blood transfusionsb | 3 (1-3) | 1 (1-1) | 1 (1-1) | 1 (1-1) |  |
| Episodes of ACS | 4 (13.3) | 1 (3.3) | 0 (0.0) | 0 (0.0) |  |
| Episodes of priapism | 2 (6.7) | 0 (0.0) | 0 (0.0 | 0 (0.0) | / |
| Neurologic incidents  | 5 (16.7) | 0 (0.0) | 1 (3.3) | 0 (0.0) | / |
| Weight (kg) | 22 (17.5-27.8) | 22.5 (18-27) | 23 (18-28.8) | 24 (18.8-30) | <0.001 |
| Hemoglobin electrophoresis: HbF (%) | 12.1 (7.2-18.2) | 10.5 (4.5-18.1) | 15.2 (13.6-21.6) | 20.6 (16.3-25.2) | <0.001a |
| Hemoglobin level (g/dl) | 6.7 (6.0-7.5) | 7.6 (6.9-8.3) | 8.1 (7.4-8.9) | 8.3 (7.4-9.4) | <0.001 |
| Reticulocytes (/mm3) | 272090 (179310-367900) | 174080 (99190-258787.5) | 182400122000-203200) | 167880 (101755-202325) | 0.019 |
| Mean corpuscular volume (fL) | 86.5 (80.0-94.3) | 91.0 (85.5-101.5) | 92.0 (87.0-103.0) | 96.0 (87.5-100.0) | <0.001 |
| White blood cells (/mm3) | 14600 (12375-19875) | 11800 (9530-16920) | 10700 (6900-14600) | 9650 (6050-12500) | <0.001 |
| Platelets (/mm3) | 408000 (340750-525000) | 387000 (237500-490500) | 333000 (206000-368000) | 321000 (246000-419000) | 0.003 |
| Serum LDH (IU/l) | 2031 (1408-3560) | 1018 (897-/) | 1283.5 (854.8-2361.5) | 1174.5 (946.5-1457.5) | 0.019a |

Data are presented as numbers (percentage) or median (interquartile range) where appropriate; ACS: acute chest syndrome; HU: hydroxyurea; LDH: lactate dehydrogenase; VOC: vaso-occlusive crisis;

aResults of the comparison between values at HU initiation and 12 months later, due to the fact that very few patients performed these lab tests at 3 and 6 months; bthe median number of blood transfusions is given per year before HU initiation, and within the period for other timelines

**Adverse effects and adherence to medication**

Concerning adverse effects, no patient reported headaches or nausea; one case of transitory vomiting was recorded (3.3%), one case of cutaneous xerosis (3.3%), and one case of nails hyperpigmentation (3.3%). No patient (or patient's parent) had any fear about taking the drug, not even with the knowledge of the risk of infertility.

Further, HU was interrupted among 24 patients (80%), though for less than one month during the 12 months of follow-up. The main reasons for this interruption were: shortage of HU at pharmacies (56.7%), lack of money to buy the drug (20%), and patients' whims (6.7%).

**DISCUSSION**

This study is among the first in Cameroon to establish the valuable impact of HU in SCD children and adolescents. We recruited 30 patients who had been placed on HU subsequent to one or more clear indications and followed-up until 12 months after drug initiation. Despite drug interruption, mainly due to shortage in pharmacies and lack of money, there was a substantial improvement in clinical and biological parameters: the number of complications (hospitalizations, severe VOC, blood transfusion, ACS, priapism and neurologic incidents) decreased as well as the number of reticulocytes, white blood cells, platelets, and serum LDH titers. On the other hand, there was a significant increase in the weight, HbF percentage, hemoglobin and mean corpuscular volume levels. The drug was well-tolerated and no fear regarding the risk of sterility was reported. Therefore, it is high time HU be introduced in routine clinical care in our country; though it should be prescribed by experienced hands after proof of necessity, and patients/parents should be educated and continuously followed-up to monitor adverse effects.

The median age and the size of our sample are close to those reported in the Mellouli et al study, with median age 9 years (range 2-18 years) and 27 patients [10]. The small size of our study population could be explained by several factors: the unavailability of HU, the elevated cost of the drug, the financial difficulties of the families leading to the non-completion of follow-up biological examinations, hence a high exclusion rate of the files. Indeed, this study was not funded; drug costs and follow-up exams were the sole responsibility of the parents. Efforts could be made to subsidize HU in SCD, or even follow-up examinations as is done in other chronic conditions such as HIV. This would make HU more available and affordable.

We noticed an improvement in clinical parameters: such as a reduction in severe vaso-occlusive crises, a decrease in transfusion needs, a reduction in the occurrence of acute chest syndromes, the number and duration of hospitalizations. These findings are coherent with the literature on the subject [11, 12, 13, 14, 15, and 16]. This can be explained by the mechanism of action of HU: increase in fetal hemoglobin synthesis, induction of nitric oxide synthesis, decrease of red blood cell adhesion to vascular endothelium, modulation of inflammatory phenomena [17, 18, 19, 20]. All this is reflected clinically by a decrease in the severity of the disease [12]. Due to clinical improvement, we observed a reduction in the number of days of hospitalization after one year (median of 7 vs 2 days). These data are similar to those of Gulbis in 2004 and Mellouli in 2013, who reported a considerable reduction in average duration of stay [10, 15].

Similarly, the number of blood transfusions decreased from a median of 3 transfusions/year to a single transfusion after 1 year; in addition, the number of people requiring a transfusion also decreased. These results are close to those of Charache et al. in the United States in 1995 [19] and those of Mellouli [10] et al. in 2013, where the mean transfusion rate decreased from 1.6 transfusions/patient/year to 0.15 transfusion/patient/year. This can be explained by the increase in baseline hemoglobin and hemoglobin F [21, 22, 23].

For biological parameters, a significant increase in fetal hemoglobin, from a median of 12% to 21%, was found in our study, an increase of nearly 9%. This increase is within the range of values ​​found by Mellouli et al. (3 to 30%) [10]. similarly, we recorded a significant increase in hemoglobin levels after one year (median 6.7 vs 8.3 g/dl, p <0.001). At the same time, there was a significant decrease in serum LDH levels (median 2031 vs 1174 IU/l, p = 0.019), which marked a considerable reduction in hemolysis [16, 18, 20]. We noticed a reduction in the number of leukocytes (median 14600 vs 9650, p <0.001) and platelets (median 408 000 vs 321 000 / mm3, p = 0.003), thus contributing to the reduction in blood viscosity and risk of thrombosis secondary to hypercoagulation [21, 22]. These findings are similar to those of Mellouli, Ferster, and Zimmerman [10, 14, 16, and 19].

With regards to mean corpuscular volume, values increased significantly after one year, from a median of 86.5 to 96 fL. This result is close to that of Ferster et al, who observed an increase of 85.2 to 95.5 fL on average, after ... [16, 18]. The decrease in the number of reticulocytes found in this study is similar to those reported by Mellouli [15]. This decrease could be explained by the fact that HU causes an increase in baseline hemoglobin with a reduction in hemolysis and consequently a less active bone marrow [15, 20, 21, and 22].

These results also testify to the good tolerance of HU in our patients (absence of depression of medullary activity), which could be related to the low doses of the HU used in our series (about 22,4mg/kg). Also further showing the good tolerance of the drug, we have recorded only minimal adverse effects, occurring a few times, in line with previous observations [14, 24]. Clinicians should therefore be encouraged to prescribe this drug if indicated, and patients/parents educated and reassured to give up their fears and apprehensions about the drug.

However, our findings should be interpreted in the context of some limitations. First, we collected our data retrospectively, which implied missing information, precluded from the reporting of the results of the patient/time of follow-up and from investigating other parameters. Second, the absence of a control-arm not taking HU hinders from concluding that what we observed as changes are solely the effects of treatment with HU; it is true nonetheless that this would have posed a serious ethical issue. Third, the changes we observed in this sample of SCD children and adolescents may be underestimated, when we consider that almost 80% of them interrupted their medication for one reason or the other. Specifically, the study was not funded, which excluded many patients presenting clear indications from initiating HU. Additionally, pharmacists, who were afraid of not being able to selling the drug, did not order it in sufficient quantities, resulting in shortages. Finally, many parents did not have sufficient financial resources to perform all the required laboratory exams, which contributed to rejection of many incomplete patients' files, hence a low sample size.

**CONCLUSION**

After 12 months, hydroxyurea considerably reduced major SCD complications, significantly improving clinical and biological parameters. Moreover, and interestingly, the drug was well tolerated, with very few and harmless adverse effects. Therefore, it is high time HU be introduced in routine clinical practice for SCD patients in our context. However, the drug should be prescribed by experienced hands after proof of necessity, and patients should be educated and continually monitored.

**Acknowledgement**

To patients and family.

**Author’s contribution**

Bibliographic research: ANAY, SSNU, OIH.

Study design: ANAY, SSNU, OIH

Data collection: OIH, ANAY, JMS, EW, SAT

Stat analysis: JRN, OIH, ANAY

Reviewing: POKN, SSNU, ANAY, OIH, JRN, SAT, JMS

**REFERENCES**

1. Organisation Mondiale de la Santé : rapport 2006 de la cinquante-neuvième assemblée mondiale de la santé. A59/9, Genève. Disponible sur : <http://apps.who.int/gb/ebwha/pdf_files/WHA59-REC1/f/WHA59_2006_REC1-fr.pdf>.
2. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World HealthOrgan. 2008; 86:480-7.
3. Nga AC. Dépistage néonatal de la drépanocytose au Cameroun. Etude rétrospective sur 5846 nouveau-nés au Centre Hospitalier d’Essos. [Mémoire : Pédiatrie]. Yaoundé : Université de Yaoundé I ; 2013.
4. Dépistage néonatal de la drépanocytose au Cameroun. Etude pilote réalisé par le groupe d’étude de la drépanocytose au Cameroun et l’Institut Européen pour le développemen et la copération. En cours et non encore publiée.
5. Galacteros F. Drépanocytose. In : « Encyclopédie Orphanet » [Consulté le 17 sept 2013]. Disponible sur : [www.orpha.net/data/patho/FR/fr-drepanocy.pdf](http://www.orpha.net/data/patho/FR/fr-drepanocy.pdf).
6. Girot R, de Montalembert M. Drépanocytose chez l’enfant. EMC (Elsevier SAS, Paris), Pédiatrie, 4-080-A-20, 2006.
7. Gulbis B, Haberm D, Dufour D et al. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events.Blood. 2004; 105: 2685-90.
8. Steinberg M.H, Barton F, Castro O. et al. Effet of hydroxyurea on mortality and morbidity in adult sickle cell anemia. Risk and benefits up to 9 years of treatment. JAMA, 2003; 289: 1645-51.
9. Zimmerman SA, Schultz WH, Ware RE et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood.2004; 103:2039-45.
10. Mellouli F, Chouaibi S, Dhouib N, Ouederni M, Ben Khaled M, Abbes S, Béjaoui M L. Efficacité et tolérance de l’hydroxyurée dans les formes graves de la drépanocytose : étude prospective de 65 cas. Tunis Medi.2013; 91: 544-550.
11. 11-Sow AD.Etude des répercussions de la drépanocytose SS sur les phénomènes de croissance et de maturation dentaire chez l’enfant [Thèse: Odontologie]. Dakar: Université Cheikh AntaDiop de Dakar; 2006.
12. Mutoke Nkashama G, Kanteng A, Wakamb G, Mutombo Mulangu A, Mutoke Nkashama G, Kabeya Kupa B, Luboya Numbi O. De l’hémoglobine SS à SF: Intérêt de l’hydroxyurée dans la prise en charge de la drépanocytose chez 2 enfants congolais et revue de la littérature. The Pan African Medical Journal. 2015; 21:124
13. Enyama D. Evolution clinique et hémathologique d’enfants drépanocytaires homozygotes traités par l’hydroxuré à Yaoundé. [Thèse Méd]. [Yaoundé]: Université de Yaoundé I; 2005.
14. Wang WC, Ware RE, Miller ST, et al. Baby hug investigators Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, conttroled trial. Lancet. 2011; 377 (9778): 1663-72
15. Gulbis B, Haberm D, Dufour D et al. Hydroxyurea for sickle cell disease in children and for prevention of cerebrovascular events. Blood. 2004; 105: 2685-90.
16. Ferster A, Tahriri P, Vermylen C et al. Five years of experience with hydroxyurea in children and young adults with sickle cell disease. Blood. 2001; 97:3628-32.
17. llery C A, Du MC, Wang C, Scott J P. Hydroxyurea therapy decreases the in vitro adhesion of sickle erythrocytes to thrombospodin and lamini. Br J Haematol. 2000; 109: 322-27.
18. Benkerrou M, Delarche C, Brahimy L, et al. Hydroxyurea corrects the dysregulated L-slectin expression and increased H2O2 production of polymorphonuclear neutrophils from patients with sickle cell aenemia. Blood.2002; 99: 2297-03.
19. Charaches S, Terrin ML, Moore RD, Dover GJ, Barton FB, Echert SV, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med.1995; (2):1317-22.
20. Charache S, Dover GJ, Moore RD, Eckert, Koshy M, Ballas SK, et al Hydroxyurea: effects on haemoglobin F production in patients with sickle cell anaemia. Blood. 1992;79(10):2555-65
21. Hjankins JS, Ware RE, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the Husoft extension study. Blood. 2005; 106 (7): 2269-75.
22. Strousse JJ, Lanzkrons S, beach MC, et al. Hyoxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. Pediatrics. 2008;122 (6): 1332-42 .
23. Steinberg M.H, Barton F, Castro O. et al. Effet of hydroxyurea on mortality and morbidity in adult sickle cell anemia. Risk and benefits up to 9 years of treatment. JAMA, 2003; 289: 1645-51.
24. Wang WC, Wynn LW, Rogers ZR, Scott JP, Lane PA, Ware RE. A two-year pilot trial of Hydroxyurea in very young children with sickle cell anaemia.J Pediatr. 2001;139(6): 790-6.