Effect of Hydroxyurea in Children With Sickle Cell Disease in Saudi Arabia

Zakaria Mohammed Al Hawsawi CABP
Waheed Ahmed Turkistani CSBP

Department of Pediatrics
Madina Maternity and Children's Hospital
Al Madina Al Munawara, Kingdom of Saudi Arabia

Abstract

Objective
The objective of this study is to demonstrate the effects of hydroxyurea in children with sickle cell disease at Madina Maternity and Children's Hospital and to evaluate its short term safety.

Methods
This was a retrospective review over two years period from 2004 – 2006.

1. Children with sickle cell disease who had three or more attacks of painful crisis per year
2. Children with sickle cell disease who had two or more episodes of acute chest syndrome per year.

The dose range of Hydroxyurea was 15 – 30 mg/kg/day. The clinical episodes and the laboratory investigations were monitored monthly.

Results
The total patients included initially were 14; 4 patients were excluded because of poor compliance to treatment. 10 patients were eligible for the study. 6 were male and 4 were female. 8 patients were Saudi and 2 patients were non Saudis. The age range was 5 – 15 years. The attacks of painful crisis and acute chest syndrome were significantly reduced after Hydroxyurea treatment, also laboratory investigation showed significant increase in MCV and Hemoglobin F values after Hydroxyurea.

Conclusion
We conclude that Hydroxyurea is effective in children with sickle cell disease and had no major short term adverse effect. However long terms follow up is required to evaluate long term adverse effect.

Key words: Hemoglobin F, Hydroxyurea, Sickle cell disease

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Correspondence to:
Dr. Zakaria Mohammed Al Hawsawi
Consultant Pediatric Haematologist Oncologist
Clinical Assistant Professor Taibah University
Department of Pediatrics, Madina Maternity and Children's Hospital
6205 Al Madina Al Munawara
Kingdom of Saudi Arabia
Tel +966 4 8640927
Email zhawsawi@yahoo.com
Introduction

Sickle cell disease is one of the most common hereditary disorders worldwide, the basic defect result from the substitution of valine for glutamic acid at the sixth position of β-globin. The sickle cell gene is prevalent in West Africa, Central Africa, The Mediterranean, the Middle East and certain parts of India. Sickel cell disease is a health problem in certain parts of Saudi Arabia in the Eastern, Western and the South West province. In Madina the estimated prevalence of sickle cell anemia (Hbss) is 0.01 and the carrier rate (HbAs) is 0.087, and it is of severe Benin haplotype.

One of the common hospital presentations of SCD in our institute are painful crisis and acute chest syndrome. Hydroxyurea (HU) is an antimetabolite agent, the mechanism by which it produce beneficial effects in patients with SCD is uncertain, however it is believed that it work by increasing the production of fetal haemoglobin in red blood cells, decreasing neutrophil, increasing water content of RBCs, increasing deformability of sickle cells and altering the adhesion of RBC to endothelium.

There were various studies about the effect of HU in adult and children with SCD which showed significant reduction in the frequency of painful crisis, acute chest syndrome, hospitalization, and the need for blood transfusion.

The objective of this study is to demonstrate our experience with Hydroxyurea in children with sickle cell disease and to determine its beneficial effect and short term safety.

Materials and Methods

Children with severe sickle cell disease followed at Paediatric Haematology unit in Madina Maternity & Children’s Hospital from February 2004 to February 2006, ages 5 - 15 years were enrolled in the study. Severe disease was defined as follows:

1. 3 or more painful crisis per year within two years before study entry.
2. 2 or more episodes of acute chest syndrome (ACS) per year requiring hospital admission within the two years before study entry.

Exclusion criteria included age less than 5 years, poor compliance to medication, serum creatinine greater than 1.0 mg/dl, serum alanine transferase (ALT) more than twice the upper limit of normal. Before enrollment informed consent was obtained from the parents. The dose range of Hydroxyurea was 15 to 30 mg/kg/day. Patients initially started on 15 mg/kg orally as a single daily dose. The daily dose was increased by 5 mg/kg every 8 weeks in the absence of toxicity. Toxicity was defined as one or more of the following:

1. Absolute neutrophil count ANC below 2000 x 10⁶/L
2. A decrease in haemoglobin concentration by 20% from the steady state or Hb < 5 g/dl.
3. A platelet count less than 80.000 x 10⁶/L
4. An ALT value greater than twice the upper limit of normal
5. 50% increase from baseline in serum creatinine or value of more than 1.0 mg/dl

If toxicity occurs, HU was stopped for at least 1 week, once the toxicity resolved; treatment will then be resumed at a dose of 2.5 mg/kg lower than the dose at which the toxicity occurred. An adverse event was defined as death or any life-threatening event.

The patients were monitored monthly at outpatient's clinic visits interval histories, physical examination and laboratory results were recorded. Statistical analysis was performed with electronic web chi square calculator. P value was significant, if equal or less than 0.05.

Results

14 patients were enrolled in the study, 4 patients were excluded because of poor compliance to HU. The total number of patients included in the study was 10
Hydroxyurea and sickle cell disease in children

patients; 6 male and 4 female. Eight patients were Saudi and 2 patients were non Saudis. Age range was 5 – 15 years with mean age of 12 years. Table 1 summarizes the clinical and laboratory data at baseline and after Hydroxyurea treatment. The table shows that the number of painful crisis significantly decreased after Hydroxyurea treatment from 70 episodes to 25; P value < 0.05 , while the number of ACS decreased from 8 to zero after Hydroxyurea with P value < 0.025. 90% of patient’s Hb increased at least 1 gm/dl after HU treatment. 80% of patients showed significant increase of mean corpuscular volume (MCV) after HU therapy. 75% of those who had available result of HbF Hydroxyurea showed significant increase of HbF on HU therapy. The laboratory monitoring did not show evidence of haematological, hepatic or renal toxicities and no adverse events occurred.

Table 1: Clinical and Laboratory Finding; baseline and on Hydroxurea treatment

<table>
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<th>Number of patients</th>
<th>Age</th>
<th>Sex</th>
<th>No. of Painful crisis (admission required)</th>
<th>No. of ACS</th>
<th>Hb g/dl</th>
<th>MCVFL</th>
<th>HbF %</th>
<th>WBC X10⁶</th>
<th>Platelet X 10⁶</th>
<th>No. of Painful crisis</th>
<th>No. of ACS</th>
<th>Hb g/dl</th>
<th>MCVFL</th>
<th>HbF %</th>
<th>WBC X10⁶</th>
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Hb = Haemoglobin blood count  MCV = mean corpuscular volume  HbF = Fetal haemoglobin  WBC= White blood count
Discussion

Hydroxyurea had been approved by the United States of America Food and Drug Administration (FDA) for use in adults who suffer from severe painful crisis. Since the multi-centers study of Hydroxyurea (MSH) in adults, there were many studies in children demonstrating the beneficial effect of HU. Hydroxyurea trial was started earlier in Saudi Arabia in adult by El Hazmi et al. Recently, AL Jam'a et al reported a study on Hydroxyurea therapy in children older than 10 years and adult in Saudi Arabia. To the best of our knowledge there was no reported study in children younger than 10 years in Saudi Arabia. Our study showed significant reduction in the number of painful crisis and acute chest syndrome, this result is consistent with beneficial effect of HU observed in other trials in adult and children. The youngest patient in our study was 5 years old; however others used HU in very young infant without serious short term complication.

90% of our patients showed a rise of hemoglobin level after HU treatment, 75% of those who had available result of HbF level showed significant increase in HbF after HU treatment consistent with well established effect of HU in children and adult with SCD. It has been well established after extensive clinical and basic research that high HbF concentration reduces the severity of SCD by preventing the formation of hemoglobin S polymers. Mean corpuscular volume (MCV) increased after HU treatment in 80% of our patients similar to others. Increasing values of MCV were parallel to the rise in HbF concentration making the MCV a useful inexpensive surrogate for HbF during therapy.

When MCV increase it improve sickle erythrocyte hydration which increase sickle cell deformability and that further contribute to the effect of HU in reducing frequency of painful crisis. Ten to 25% of SCD patients on HU treatment dose not had an increase in HbF level, perhaps because of Abnormal bone marrow, genetic factors, or variation in drug metabolism.

No haematological, hepatic or renal toxicities were observed in our study, however other studies reported limited transient toxicities which were predominantly of mild neutropenia and minimal, if any, renal or hepatic toxicity. No adverse events were observed in our patients.

Long term adverse effect of HU therapy is not yet known, but up to date no chromosomal breakage, mutation or carcinogenicity have been documented. In the adult MSH follow up study, no cases of leukemia have been observed in up to 9 years of follow up; also follow up of HU treatment in children for 7 years did not report any cases of malignancy. Another recent report of long term effects in children showed no severe side effect or malignancy related to HU therapy for 10 years. In French study 64 patients (age 5 – 45 years) with erythrocytosis caused by inoperable cyanotic congenital heart disease treated with Hydroxyurea for 2 to 15 years, reported no cases of malignancy or irreversible toxic effects.

Hydroxyurea also had a beneficial effect on preservation of splenic function. It has been reported that 47% of children had functional asplenia at age when about 80% would be expected to have asplenia by red cell pit counts after 2 years treatment with HU. Splenic regeneration has been reported in two adults with sickle cell anemia treated with Hydroxyurea. The adult MSH study suggests that HU should be considered for all patients with SCD, and the lack of significant short or long term toxicity in large cohort of children with SCD further support this recommendation.

Hydroxyurea had no adverse effects on growth in children for up to 7 years treatment and puberty was achieved normally.

In conclusion, there is substantial evidence that Hydroxyurea is very beneficial and effective drug for children with severe SCD and we recommend for all children with severe sickle cell disease in the Kingdom of Saudi Arabia. There were no serious short or long term adverse effects up to date, but
registry for long term adverse effect is required.

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