ORIGINAL ARTICLE

The Effect of Hydroxyurea Therapy on Adverse Clinical Events and Haematological Indices in Paediatric Patients with Sickle Cell Anaemia

K Maharaj, C Bodkyn, C Greene, S Bahadursingh

ABSTRACT

Objective: *The aim of this study was to determine the effect of hydroxyurea on adverse clinical events and haematological indices in paediatric patients with sickle cell anaemia.*
Method: *This study compared the same cohort of patients before and after hydroxyurea therapy, monitoring the rate of adverse events, pre- and post-treatment and haematological indices.*
Results: *Of the 40 patients, the incidence rate of painful crises post-treatment was 80% lower than pre-treatment. Post-treatment incidence rates of painful crises managed at home, requiring emergency department care or requiring admission to the ward were also lower - 79%, 81% and 84%, respectively. There was no significant difference in the incidence of other clinical events. The haemoglobin concentration increased within the first month and plateaued while the mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC) continued to increase until six months before plateauing out. The white blood cell count (WBC) and absolute neutrophil count (ANC) decreased over the first month before levels stabilized. The reticulocyte percentage and the absolute reticulocyte count (ARC) decreased over the first three months before plateauing while the platelet count remained stable.*
Conclusion: *Hydroxyurea significantly reduced the incidence of painful crises. There were significant increases in haemoglobin, MCV and MCHC with decreases in WBC, ANC, ARC, and reticulocyte percentage while the platelet count remained relatively stable.*

Keywords: Clinical adverse events, haematological indices, hydroxyurea, sickle cell disease

Efecto de la Terapia con Hidroxiurea en los Eventos Clínicos Adversos y los Indices Haematológicos de Pacientes Paediátricos con Aanemia de Células Falciformes

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RESUMEN

Objetivo: *El objetivo de este estudio fue determinar el efecto de la hidroxiurea sobre los eventos clínicos adversos y los índices hematológicos en pacientes pediátricos con anemia falciforme.*
Método: *Este estudio comparó una misma cohorte de pacientes antes y después del tratamiento con hidroxiurea, monitoreando la tasa de eventos adversos, el tratamiento previo y posterior, y los índices hematológicos.*
Resultados: *En los 40 pacientes, la tasa de incidencia de postratamiento de crisis dolorosas fue 80% inferior a la del pretratamiento. Las tasas de incidencia de postratamientos de crisis*

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 DOI: 10.7727/wimj.2015.538

dolorosas que fueron tratadas en el hogar, atendidas en el departamento de emergencias, o requirieron ingreso hospitalario, fueron también menores -79%, 81% y 84%, respectivamente. No hubo diferencias significativas en la incidencia de otros eventos clínicos. La concentración de hemoglobina aumentó en el primer mes y se estabilizó, mientras que el volumen corpuscular medio (VCM) y la concentración de hemoglobina corpuscular media (CHCM) continuaron aumentando hasta seis meses antes de estabilizarse. nivelarse. El conteo de glóbulos blancos (CGB) y el conteo absoluto de neutrófilos (CAN) disminuyeron durante el primer mes antes de que los niveles se estabilizaran. El porcentaje de reticulocitos y el conteo absoluto de reticulocitos (CAR) disminuyeron durante los primeros tres meses antes de estabilizarse, mientras que el conteo de plateletas permaneció estable.

Conclusión: *La hidroxiurea redujo significativamente la incidencia de crisis dolorosas. Hubo aumentos significativos de hemoglobina, VCM y CHCM con disminuciones de CGB, CAN, CAR, y porcentaje de reticulocitos mientras que el conteo plaquetario permaneció relativamente estable.*

Palabras clave: Eventos adversos clínicos, índices hematológicos, hidroxiurea, enfermedad de células falciformes

West Indian Med J 2019; 68 (2): 81

INTRODUCTION

Sickle cell anaemia (SCA) is the most important potentially devastating, recessively inherited condition. Sickle cell anaemia is characterized by haemoglobin (Hb) polymerisation that results in sickle-shaped red blood cells, vaso-occlusion, haemolysis and vasculo-endothelial dysfunction, causing pain, anaemia, organ injury and early mortality. Disease severity varies widely but overall mortality is substantially increased and life expectancy decreased when compared with the general population. Despite the well-described genetics and pathophysiology of SCA, clinical care for affected individuals has been mostly supportive, typically including intravenous hydration, analgesics, antibiotics and red blood cell transfusions.

Clinical symptoms begin in the first year of life with the physiologic decline in fetal haemoglobin (HbF) concentration, but higher levels of HbF have been associated with fewer pain crises (1) and improved survival (2). Hydroxyurea, an antineoplastic agent that inhibits ribonucleotide reductase, increases HbF in red blood cells and has other potentially beneficial effects, including improved nitric oxide metabolism, reduced red-cell-endothelial interaction and decreased erythrocyte density (3). Hydroxyurea is the only widely used drug, which modifies disease pathogenesis.

The most recent evidence supporting the use of hydroxyurea in children comes from the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG). This was a multi-centre, randomized, double-blind, placebo-controlled study of daily oral hydroxyurea in children with SCA (HbSS and Sß0 thalassemia), 9 to 18 months of age. There were significantly less clinical events in the hydroxyurea group including painful events, acute chest syndrome (ACS), hospitalizations, and transfusions. Based on the results of the BABY HUG trial, the authors concluded that hydroxyurea could be considered for paediatric patients (4).

The Hydroxyurea Study of Long Term Effects (HUSTLE) is a prospective observational study of children with SCA treated with hydroxyurea based on clinical severity, which attempts to evaluate the long-term cellular and molecular effects of hydroxyurea. Reports have not identified any evidence of cumulative chromosomal damage in the hydroxyurea-exposed group with up to 12 years of treatment exposure (5). In addition, extended follow-up from a small teenage cohort from HUSOFT (with 14 years of treatment since infancy) indicated good health, normal growth and development, and no evidence of myelodysplasia or malignancy (6).

The haematological effects of hydroxyurea therapy are closely linked to clinical benefits, but also are the parameters used for dose escalation to maximum tolerated dose. Laboratory effects include a predictable rise in the haemoglobin concentration, HbF percentage, and mean corpuscular volume along with a concurrent decrease in absolute reticulocyte count, total leukocyte count and absolute neutrophil count. These laboratory values, in addition to examination of the peripheral blood film for erythrocyte morphology, are used to escalate

patients to maximum tolerated dose, and also can be used to monitor medication adherence (7). These laboratory effects have been demonstrated to be consistent and sustainable in both adults and children with SCA (8, 9).

Trinidad and Tobago has a large Afro-Caribbean paediatric population with a high prevalence of SCA. The paediatric hospital at the Eric Williams Medical Sciences Complex (EWMSC) is the largest centre for the management of SCA patients in Trinidad and Tobago. Based on the positive findings in the recent literature, many of these children have been started on hydroxyurea in an attempt to reduce the number of hospitalizations for disease-related events. Although hydroxyurea is widely available in our setting, there are dosing limitations. It is only available as a 500 mg capsule preparation and the recommended daily dose in children is 20–30 mg/kg/day, therefore, to ensure that patients get an adequate dose, alternate day dosing is required in many cases. No studies have yet been done in our population, however, to determine the outcome of this intervention or to assess the impact on clinical status.

The aim of this study was to determine the effect of hydroxyurea therapy on adverse clinical events and haematological indices in paediatric patients with sickle cell anaemia attending the Paediatric Haematology Clinic at EWMSC.

METHOD

The study is a retrospective cohort study. It compares the same cohort of patients before and after hydroxyurea therapy, monitoring the rate of adverse events pre- and post-treatment, and follows haematological indices of the cohort over time, from initiation of treatment. A consecutive convenience sampling method was used to obtain patients for the study, which included only patients with sickle cell anaemia on hydroxyurea attending the Paediatric Haematology Clinic at EWMSC from 2007–2013, ages of 1 year to 15 years. Only patients who were compliant, had no other chronic medical conditions and received standard age-appropriate care for their disease including penicillin prophylaxis, folic acid, pneumococcal immunization and parental education were included in this study.

Data collected included demographic data, clinical events and haematological indices. Parents were interviewed to determine the pre- and post-treatment rates of adverse clinical events. Adverse clinical events included known complications of sickle cell anaemia, such as painful events, dactylitis, acute chest syndrome, stroke, priapism, sepsis/bacteraemia and osteomyelitis. The haematological indices investigated were haemoglobin concentration, mean corpuscular volume, mean corpuscular haemoglobin, white blood cell, neutrophil count, platelet count, and reticulocyte count.

The mean and standard deviation (SD) were used to summarise continuous normally distributed variables, while the median and interquartile range (IQR) were used for skewed variables. The rate ratio (RR) was used to compare the pre- and post-treatment incidence rate of events; RR estimates and their 95% confidence intervals were derived in a Poisson regression model using the robust clustered estimator of variance. The paired *t*-test was used to test the mean difference in haematologic indices between pairs of time points. Ethics approvals were obtained from The University of the West Indies and the North Central Regional Health Authority.

RESULTS

Of the 280 patients with sickle cell anaemia attending clinic, 50 were on hydroxyurea, 40 (80%) met the study criteria. The median age at initiation of treatment was seven years (IQR 6; range 3 to 15). Twenty-two (55.0%) were male and 18 (45%) were female. Thirty-two (80.0%) were HbSS, 5 (12.5%) were HbSC and three (7.5%) were HbSβ Thalassemia. Mean haemoglobin concentration at baseline was 7.7 g/dL (SD 1.0). The average dose of hydroxyurea was 21 mg/kg (SD 4). Eleven (27.5%) children were on an alternating day regimen (500 mg every other day or 500 mg alternating with 1000 mg daily), while 29 (72.5%) were on a daily regimen.

Painful crises were the most commonly reported adverse clinical event and so this was analysed separately. The total pre-treatment and post-treatment follow-up times for painful events were 480 and 373 person/months, respectively. For rarer events, the total pre-treatment and post-treatment follow-up times were 3809 and 1196 person/months, respectively: total pre-treatment follow-up time was 3.2 times total post-treatment follow-up time; pre-treatment follow-up time ranged from 35 months to 181 months with median 87.5 months (IQR 67), while the post-treatment follow-up time ranged from three months to 122 months with median follow-up time of 21.5 months IQR (36.5 months).

Pre- and Post-treatment Incidence Rates of Clinical Adverse Events

For pre-treatment, the incidence rate of painful events was 21.4 events per 12 person/months of follow-up. Post-treatment rate was 4.2, 80% lower (RR 0.20; 95%

CI: 0.11, 0.35); see Table 1. For post-treatment, the incidence rate of painful crises managed at home, requiring emergency department care or requiring admission to the ward was 79% (RR 0.21; 95% CI: 0.11, 0.40), 81% (RR 0.19; 95% CI: 0.06, 0.56) and 84% (RR 0.16; 95% CI: 0.09, 0.28) lower than their respective pre-treatment incidence rates.

There was no evidence at the 5% level that the treatment effect of HU on the overall rates of painful crises (p = 0.223), or on the rate of painful crises requiring home (p = 0.162), emergency room (p = 0.592) or ward care (p = 0.991) was different in those on a daily and on alternating day regimens of HU.

Table 2 compares the pre- and post-treatment incidence rates, expressed per 18 persons/years of follow-up, of the rarer events associated with sickle cell anaemia. While the rates of these rarer events were generally observed to be lower post-treatment, there was no statistical evidence of any significant differences.

Table 1: Comparison of pre- and post-treatment incidence rates of painful crises

	Incidence Rate pre-treatment (per pyr)	Incidence Rate post-treatment (per pyr)	Rate	Ratio (95% CI)	*p*-value
Painful crises					
Any type	21.4	4.2	0.20	(0.11 , 0.35)	< 0.001
Managed at home	16.2	3.4	0.21	(0.11 , 0.40)	< 0.001
Requiring ED care	1.6	0.3	0.19	(0.06 , 0.56)	0.003
Requiring ward admission	3.5	0.6	0.16	(0.09 , 0.28)	< 0.001

Table 2: Comparison of pre- and post-treatment incidence rates of rarer events

Event	Incidence Rate Pre-treatment (per 18 pyr)	Incidence Rate Post-treatment (per 18 pyr)	Rate Ratio (95%CI)			*p*-value
ACS	1.42	0.54	0.38	(0.12	, 1.25)	0.111
Pneumonia	2.55	1.99	0.78	(0.32	, 1.90)	0.583
Stroke	0.28	0				
Osteomyelitis	0.17	0				
Dactylitis	1.30	0				
Priaprism	0	0				
Bacteremia	0	0				
Top up transfusion	3.18	3.07	0.97	(0.36	, 2.59)	0.947
Exchange transfusion	1.42	0.36	0.25	(0.06	, 1.07)	0.062

Changes in Haematologic Indices

Haemoglobin (Hb), Mean corpuscular volume (MCV), Mean corpuscular haemoglobin concentration (MCHC), White blood cell count (WBC), Absolute neutrophil count (ANC), Reticulocyte percentage (%) and Absolute reticulocyte count (ARC) were measured at base-line and then at 1, 3, 6, 12 and 24 months after starting HU (Table 3).

Table 3: Mean of each haematologic index at each time point after initiation of treatment

Haematologic Index	Baseline	1 month	3 months	6 months	12 months	24 months
Haemoglobin concentration (g/dL)	7.72	8.38	8.27	8.14	8.13	8.37
Mean corpuscular volume (fL)	74.94	80.33	81.48	85.33	85.86	87.38
Mean cell haemoglobin concentration (g/dL)	33.38	33.57	33.95	34.58	34.20	34.08
Platelet count x 10^3/μL	341.38	318.13	317.83	306.96	354.26	343.26
White blood cell count x 10^3/μL	17.09	11.90	12.09	11.90	10.90	10.86
Absolute neutrophil count x 10^3/μL	8.29	4.58	4.50	4.37	4.50	5.21
Reticulocyte %	11.04	8.61	7.53	8.11	9.95	8.63
Absolute reticulocyte count x 10^6/μL	0.33	0.26	0.21	0.24	0.27	0.24

Table 4 shows the increment and time to apparent stabilisation of changes in each of the haematological indices. There was no statistically significant change past the points stated. There was no significant change in platelet count in this cohort of patients.

DISCUSSION

The primary objective of this study was to compare clinical events in patients before and after hydroxyurea therapy. The results demonstrated that the incidence rate of painful crises post-treatment was significantly reduced with hydroxyurea in all settings, which is in keeping with the literature. This has important implications on the quality of life of patients and parents. Recurrent pain from sickle cell disease can be a significant and disabling problem (10). Interestingly, the results also indicated that the treatment effect of hydroxyurea on the overall rates of painful crises was similar in those on a daily and on alternating day regimens of the drug in all settings. This is particularly important since, to our knowledge, there have been no previous studies using alternate day dosing of hydroxyurea or detailed studies of pharmacokinetic behaviour of hydroxyurea. This lends support to continued use of hydroxyurea in our local setting with the limitation of the 500 mg capsule presentation. Rarer clinical adverse events had a higher incidence rate of the event in pre-treatment than in post-treatment but with no significant difference. This may be due to the small numbers in the study cohort or the need for longer follow-up.

The incidence rate of top-up transfusions, however, appeared to be similar in pre- and post-treatment. In the pivotal randomized trial upon which the FDA based its approval of hydroxyurea, adult patients taking hydroxyurea were found to require fewer transfusions than those who were not on hydroxyurea (11). This would be the expected trend in children as well and perhaps if this cohort was followed for a longer period the outcome may have been different.

From the results obtained it was clear that the laboratory efficacy of hydroxyurea became evident during the first to sixth months of treatment and the benefits were then sustained when children with SCA were adherent with therapy. There were significant increases in haemoglobin, MCV and MCHC with decreases in WBC, ANC, ARC and reticulocyte percentage while the platelet count remained relatively stable throughout the follow-up period. Of note, no patients experienced severe neutropenia or thrombocytopenia requiring dose adjustment or discontinuation of hydroxyurea on either dosing regimen. All patients on hydroxyurea currently have complete blood counts done every three to six months after the initial few months of treatment. Given the results of this study, this may no longer be deemed necessary.

In conclusion, the effect of hydroxyurea therapy in our population was similar to that found in the literature. There was a significant decrease in the incidence of painful crises once therapy was initiated and this was evident with daily dosing as well as alternate day dosing. There was no significant decrease in the incidence of any other adverse clinical events. No patients in the cohort experienced severe neutropenia or thrombocytopenia requiring dose adjustment or discontinuation of hydroxyurea. The vast majority of available evidence on the efficacy, effectiveness and safety of hydroxyurea in childhood SCA is from high-income countries and for children with high-quality, supportive care. The conclusions drawn from this study would be useful in guiding hydroxyurea use in other less developed countries with limited resources.

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Table 4: Increment and time to apparent stabilisation of haematological indices

Haematologic Index	Time to apparent stabilisation (months)	Mean increment from baseline	SD of increment	*p*-value
Haemoglobin concentration (g/dL)	1	0.65	1.0	< 0.001
White blood cell count x 10^3/μL	1	-5.3	7.2	< 0.001
Absolute neutrophil count x 10^3/μL	1	-3.3	6.2	0.008
Reticulocyte %	3	-2.0	3.2	0.037
Absolute reticulocyte count x 10^6/μL	3	-0.1	0.14	0.009
Mean cell haemoglobin concentration (g/dL)	6	1.6	2.4	0.003
Mean corpuscular volume (fL)	6	8	6.8	< 0.001

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