Scholars LITERATURE

La Prensa Medica Argentina

Research Article

DOI: https://doi.org/10.47275/0032-745X-326
Volume 107 Issue 3

Antimetabolite Drug in Patients with Sickle Cell Diseases in Hematological Center of Kerbalaa Training Hospital

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Abstract

Background: The antimetabolite drug increase fetal hemoglobin level and reduce the frequency of crisis in sickle cell disease patients.

Aim: To evaluate the effect of antimetabolites (hydroxyurea) in cases with frequent sickling crisis of sickle cell disease and non-transfusion dependent thalassemia in Karbala training hospital from April 2016 till December 2020.

Patient and methods: From eighty-one patients conducted in this case control study, forty were received hydroxyurea and the other forty-one patients were not. monitoring every two weeks in the first three months by sending for investigations (Hb, WBC, platelet count and blood urea and serum creatinine) in addition to assessment of drug side effects. The remaining forty-one patients who refused drug therapy we consider them as a control group.

Result: The case group who received hydroxylurea had crisis mostly after 12 weeks from last crisis, whereas the control group had crisis mostly each 3 to 7 weeks in P value 0.0001. There was no side effect in 77.5% of cases received hydroxyurea. The remaining 22.5% of cases had less or nonspecific side effects.

Conclusion: In patient with sickle cell diseases who suffered from recurrent episodes of crisis, Hydroxyurea therapy significantly decreases the frequency of the painful crisis, with low level of side effects in comparison with control group.

Keywords: Antimetabolites; Sickle Cell Disease; Hemoglubinopathies; Hydroxyurea

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Citation: Oday Abdul Ridha Mohammed Al Nasari, Ahmed Tawfeeq Abbas, Saad Ighdayyir Fenoori (2021) Antimetabolite Drug in Patients with Sickle Cell Diseases in Hematological Center of Kerbalaa Training Hospital. Prensa Med Argent, Volume 107:3. 326. DOI: https://doi.org/10.47275/0032-745X-326

Received: February 14, 2021; **Accepted:** February 22, 2021; **Published:** February 27, 2021

Introduction

Sickle cell disease is generally mean the conditions associated with the sickling process, whereas the term sickle cell anemia is usually used to describe homozygosity of hemoglobin S (i.e. HbSS). The HbSS is more severe form, HbSC of intermediate severity (combined heterozygosity for hemoglobin S and C), and less severe in those with sickle cell trait (heterozygosity for HbS) [1].

In sickle cell-beta thalassemia: the disease varies with the quantity of hemoglobin A, often being quite severe in patients with sickle cell-beta (0) thalassemia and less severe in patients with sickle cell-beta (+) thalassemia. There are an estimated 54,736 Childs born with combined heterozygosity HbSC disease each year worldwide [2].

Sickle cell crisis (Acute painful crisis) is the episodes of acute pain are the most common type of vasoocclusive events [1].

It is described as unremitting discomfort that can occur in any part of the body, but mostly occurs in the chest, abdomen, or any extremities. This painful episode is often abrupt and causes difficulty of doing the daily life activities and it is heavy on children and their caregivers.

The etiology of pain is unknown exactly, and the pathogenesis are started when blood flow is disrupted in the microvasculature by sickled cells, resulting in ischemia to the tissue that supplied by it. the risk factors for development and initiation of it may be physical stress, infection, dehydration, hypoxia, local or systemic acidosis, exposure to cold, and longtime swimming [3].

Hydroxyurea is part from an antimetabolite drugs that shown in adults with sickle cell disease (SCD) to increase fetal hemoglobin levels and reduce the symptoms of SCD. We hypothesized that antimetabolites therapy in children with severe (equal or more than three crises per year) sickle cell disease could improve hematologic parameters and decrease frequency of it [4].

Hydroxyurea is the only drug proven effective in decreasing the frequency of the crisis events. In children the hydroxyurea is safe and well tolerated in children over 5 years of age child.

the hydroxyurea may be considered in the certain groups of nontransfusion dependent thalassemia diseases which includes β-thalassemia intermedia, pulmonary hypertension, alloimmunized patients, extra medullary hematopoietic pseudo neoplasms and leg ulcers [5].

the beneficial effects in patients with sickle cell disease are uncertain exactly. The Known mechanism for its pharmacological effects that may contribute to its beneficial effects include:

- Increasing hemoglobin F levels in red blood cells.
- Decreasing neutrophils.
- Increasing the water content of RBCs.
- Increasing deformability of sickle cells.
- Altering the adhesion of RBCS of endothelium.

The metabolism of hydroxyurea is 60% by liver and gastrointestinal tract and the half-life of it is 2-4 hrs. and it excreted mainly in urine [6]. The starting dose should be 15-20 mg/kg once each day with an incremental dosage increase every 8 weeks of 5 mg/kg, and may reach a maximum of 35 mg/kg per dose if not reach the toxic level [3]. The patient should be checked for complete blood counts every 2 weeks for the first three months. After that; each month with hepatic and renal function studies every 2 weeks for first three months then monthly. History and physical examination regarding GIT, CNS, dermatological side effects should be evaluated monthly [5].

Hydroxyurea should be temporarily stopped and adjustment of the dose is indicated if:

- The absolute neutrophil count decrease below 2000/μL (or)
- Platelets below 80000/μL [3].

The side effect of hydroxyurea are nausea, vomiting, constipation, diarrhea, mucositis, Acute pulmonary reactions, genetic mutation, myelosuppression, secondary leukemia, hyperuricemia and renal failure, Dermatological changes (hyperpigmentation) [6], azoospermia, infertility.

contraindication of usage of hydroxyurea are severe anemia, bone marrow depression (WBC less than 2500/mm3, platelets are less than 100000/mm3, pregnancy and lactation [6].

Patients and Method

The study started at April 2015 and continue till December 2020, 81 patients conducted in case control study who had sickle cell diseases. The cases included in our study had frequent painful crisis (more than three episodes per year). From these 81 patients, 40 patients started with hydroxyurea in a dose of 10 - 20 mg/kg/day as 500mg capsule taken orally after meal. 18 of them diagnosed as sickle cell anemia,15 patients diagnosed as a sickle thalassemia syndrome and 7 had thalassemia intermedia. The remaining 41 patients who refused drug therapy considered as control and they were as the following: Monitoring of Patients on hydroxyurea every 2 weeks in the first 3 months by taking a blood sample (3 ml for each patient) investigated for HB, WBC total and differentials, platelet count (this was measured by Systemax XT -2000 i) and blood urea and creatinine (measured by Cobas Integra 400 plus). After these three months of treatment, the cases followed up according to their routine visit, or when they were seeking for medical consultation.

From whole study only 3 patients discontinue treatments because of appearance of side effect of drugs as the following: Sickle thalassemic patient stopped treatment due to complaining from nonspecific vomiting and abdominal pain after 8 days from onset of treatment, Sickle thalasemic patient discontinue treatment of unknown cause, Appearance of azoospermia after 6 months of treatment.

Results

Forty (25 males and 15 female) cases were received hydroxyurea. From which, 18 sickle cell anemia, 15 sickle thalassemia, 7 thalassemia intermedia cases. Forty-one control patients from which, 24 sickle cell anemia, 13 sickle thalassemia and four cases were thalassemia intermedia as shown in table 1.

The painful crisis in case group before receiving hydroxyurea were mainly 7-12weeks and in control group 3-7 weeks. After receiving hydroxyurea painful crisis were mainly > 12 weeks in P value 0.0001 as shown in table 2 and table 3.

Mainly there were no side effects of hydroxyurea in case group 31 patient (77.5%) others had nonspecific side effects (nausea, vomiting or fatigue) in 4 patients (10%), agranulocytosis 2 patients (5%) the remaining side effects (thrombocytopenia, azosthenia and azospermia) were of 2.5% for each one.as shown in table 4.

Table 1: Descriptive analysis of cases and controls according to diagnosis.

	cases		control	
	Number	**percentage**	**Number**	**percentage**
Sickle cell disease	18	22.2 %	24	29.6 %
Sickle thalassemia	15	18.5 %	13	16 %
Thalassemia intermedia	7	8.64 %	4	4.93 %
Total	40	49.34%	41	50.53 %

Table 2: Frequency of crisis in cases and control groups before starting hydroxyurea.

		2-3 wks	**3-7 wks**	**7-12 wks**	**<12 wks**
Number of crisis	**Control**	5-10	20-25	5-10	0-5
	Cases	10-15	10-15	15-20	0-5

Table 3: Frequency of crisis after introducing hydroxyurea.

		2-3 wks	**3-7 wks**	**7-12 wks**	**<12 wks**
Number of crisis	**Control**	5-10	20-25	5-10	0-5
	Cases	0-5	5-10	10-15	15-20

P value = 0.0001

Table 4: Number and percentage of patients in cases group with side effects of hydroxyurea.

	Number	**Percentage**
No side effects	31	77.5 %
Nonspecific side effects	4	10 %
Thrombocytopenia	1	2.5%
agranulocytosis	2	5%
azotemia	1	2.5%
Azoospermia	1	2.5%

Discussion

The significant decrease in painful crisis syndrome case group in our research goes with the research of Jain DL, et al. (2012) [9], in asian children with sickle cell disease in which it shows that there is significant decrease in no. of vasoocclusive crisis and hospitalization with hydroxyurea despite increase baseline HbF.

A multicenter randomized controlled trial by Wang W, et al. (2011) [10], shows that there were decrease in pain and dactylitis as well as a significant decrease in acute chest syndrome, hospitalization rate. Other studies that had the same conclusion with our result were Sharef SW, et al. (2013) [11], Rigano P, et al. (2013) [12], Gilmore A, et al. (2011) [13], Nzouakou R, et al. (2011) [14], Italia K, et al. (2009) [15], Voskandou E, et al. (2010) [16].

Recommendation

1. The usage of hydroxyurea in the managements of of sickle cell disease.

2. Further researchs regarding usage of hydroxyurea in young children with hemoglobinopathies.

3. We recommend further study for the reversibility of azoospermia and azosthenia after stopping hydroxyurea therapy.

4. Further study to prove malignancy associated with hydroxy urea treatments.

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