DOI: 10.7860/JCDR/2015/14807.6660

Short Communication

Internal Medicine Section

Clinical and Haematological Effects of Hydroxyurea in β-Thalassemia Intermedia Patients

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ABSTRACT

Introduction: It is well known that hydroxyurea (HU) impacts on clinical and haematologic indices in thalassemia. We aimed to evaluate the effect of hydroxyurea on clinical and haematological improvement in children with thalassemia intermedia.

Materials and Methods: After the patients' enrollment in the study their data such as transfusion, hospitalization, spleen size, visit, total Hb, HbF levels, MCV and MCH were compared before and after treatment with HU 10 mg/kg/day/for one year.

Results: In patients with thalassemia intermedia, HU significantly diminished the rate of transfusion, hospitalization, spleen size and significantly increased Hb MCH, HbF and MCV. Moreover HU was well tolerated in our patients and we got no remarkable adverse effect.

Conclusion: We divulged hydroxyurea 10 mg/kg/day during one year. This significantly increased HbF, total haemoglobin, MCV, MCH, without any remarkable adverse events.

Keywords: Adverse effects, Fetal hemoglobin, Hematologic tests, Hospitalization, Spleen, Treatment outcome

INTRODUCTION

In thalassemia intermedia, incomplete inhibition of beta-globin protein production occurs due to defective gene functions. The range of suppression differs among patients and induces the severity of disease [1]. Most patients with thalassemia intermedia are homozygotes or compound heterozygotes for beta-thalassemia, both of which beta-globin locations are involved [1]. In some cases a single beta globin is involved and the rest of the patients are normal. Therefore, patients with thalassemia intermedia show a wide spectrum of clinical and haematological abnormalities. Anaemia in patients with thalassemia intermedia is mild and the level of haemoglobin in these patients is usually about 8g/dl so they are able to have normal physical development without regular transfusions. However, hypersplenism may occur in some of these patients in the coming years and they might need splenectomy and some of them might need regular transfusion in adulthood [2].

Hydroxyurea (HU) is an important factor in synthesis of fetal haemoglobin (HbF) and increases the level of HbF markedly [3]. Hydroxyurea (HU) increases the level of gamma globin and it may be effective in patients with β-thalassemia and improves clinical and haematological abnormalities of thalassemia intermedia [4]. Most of the studies indicated that the possible mechanisms of HU are fetal haemoglobin induction, cell adhesive properties relieving and reduction of inflammation and hypercoagulability. These studies showed the positive impact of hydroxyurea in treatment of patients with thalassemia intermedia [4-6]. In this chart, we evaluated the effect of hydroxyurea on clinical and haematological improvement of thalassemia intermedia in patients referred to Shafa Hospital to address concerns about safety and effectiveness of HU.

MATERIALS AND METHODS

In this prospective study, we studied patients with thalassemia intermedia who were admitted to Shafa Hospital Ahvaz, Iran, from 2013-2014. Children aged 6 to 18 years old with thalassemia intermedia were recruited. The criteria for exclusion were active liver disease, creatinine more than 1.5 mg/dl, treatment other than Hu and lack of written consent. The study protocol was approved by ethical committee of Ahvaz University of Medical Sciences Research Center for Thalassemia and Haemoglobinopathy, moreover the study procedure was explained for all patients and written informed consents were taken; from 44 patients with thalassemia intermedia. Demographic data such as age and sex and duration of disease were recorded. We also evaluated the efficiency of hydroxyurea and clinical manifestations of patients such as spleen size, the number of visits, the number of hospitalization and the rate of transfusion. Furthermore, blood tests such as CBC, and Hb electrophoresis and Hb F measurement, liver and kidney function test were performed for all patients and total Hb, HbF levels, MCV, MCH were measured before treatment with HU. Subsequently, hydroxyurea was administered at dosage of 10 mg/kg/day for one year. At the end of study all tests were measured again and any possible adverse effects related to HU were evaluated and recorded.

STATISTICAL ANALYSIS

Data were analysed using SPSS version 21. Categorical data were presented as numbers (%), and continuous data as mean ± SD. We used the Chi-square test to compare categorical variables. $\alpha < 0.05$ was considered significant.

RESULTS

In patients with thalassemia intermedia Hu significantly, decreased the rate of transfusion and 41 patients became completely transfusion free. Moreover, HU treatment significantly decreased the rate of hospitalization, spleen size and number of transfusions, number of visits by specialist. Additionally drug treatment significantly decreased the number of patients with Hb <10, MCH <27, HbF at level of 20-25%, MCV<100fl and significantly increased Hb>10, MCH>27, HbF>25%, MCV>100fl [Table/Fig-1]. HU was well tolerated in our patients and no remarkable adverse effect occurred in patients with thalassemia intermedia.

DISCUSSION

It is well established that hydroxyurea is an antimetabolite inhibitor with cellular and haematological effects that increases total Hb, HbF, MCH and MCV [7]. Moreover, several studies indicated. HU increases the transfusion intervals of patients with thalassemia and significantly improves clinical abnormalities [1,4,8].

		Thalassemia Intermedia		p-value
		Pre treatment	Post treatment	
Transfusion	yes	33(75%)	3(6.8%)	0.001
	No	11(25%)	41(93.2%)	
Hospitalization	No	34(77.3%)	42(95.4%)	0.03
	1	2(4.5%)	1(2.3%)	
	2	6(13.6%)	1(2.3%)	
	3	2(4.5%)	0	
Visit	no	2(4.5%)	38(86.4%)	0.04
	1-2	35(79.5%)	5(11.4%)	
	3-4	7(15.9%)	1(2.3%)	
Spleen	Nl	3(6.8%)	40(91%)	0.01
	3-6cm	41(93.2%)	4(9.1%)	
Hb(g/l)	<6	4(9.1%)	2(4.5%)	0.04
	6-8	12(27.3%)	3(6.8%)	
	8-10	23(52.3%)	5(11.4%)	
	10-12	4(9.1%)	34(77.3%)	
	>12	1(2.3%)	0	
MCH	<20	7(15.9%)	2(4.5%)	0.03
	20-27	25(56.8%)	4(9.1%)	
	27-30	8(18.2%)	13(29.5%)	
	>30	4(9.1%)	25(56.8%)	
HbF	<5%	1(2.3%)	1(2.3%)	0.03
	5-10%	1(2.3%)	1(2.3%)	
	15-20%	2(4.5%)	1(2.3%)	
	20-25%	11(25%)	8(18.2%)	
	>25%	29(65.9%)	33(75%)	
MCV	<80	30(68.2%)	5(11.4%)	0.01
	80-100	12(27.3%)	3(6.8%)	
	>100	2(4.5%)	36(81.8%)	

[Table/Fig-1]: Clinical manifestations and haematologic index in patients with thalassemia intermedia

In this study, 44 patients with thalassemia intermedia were treated with hydroxyurea 10 mg/kg/day for one year and showed that HU significantly decreased the rate of transfusion, hospitalization, spleen size and number of visits by specialist, moreover improved the level of Hb, MCH, HbF and MCV. Additionally we demonstrated that HU treatment was safe without significant adverse effects in children. Our findings are supported by Hashemi et al., that evaluated the effect HU on transfusion requirements in patients with major and intermediate thalassemia and indicated HU decreases regular transfusion requirement. Moreover, they emphasized HU treatment is safe without remarkable adverse events in children [6,9]. However, a study by Ghasemi et al., evaluated the side effects of hydroxyurea in patients with thalassemia major, intermedia and sickle cell disease and designated some adverse event such as dermatologic (39.28%), neurologic (23.2%), gastrointestinal (17.5%) and haematologic (10.71%) in their patients. Although they detected these adverse effects, but emphasized that side effects were transient and not significant and HU was well tolerated by all patients [10]. In agreement to our findings another study by Zamani et al., presented that HU 10mg/kg/day increased the level of Hb and decreased the rate of transfusion in 49 patients with β-thalassemia. Furthermore they found no notable adverse effect and no malignancy in five years follow up, only they reported one case of transient thrombocytopenia [11]. We divulged hydroxyurea improves the level of HbF. The valuable effects of HU includes fetal haemoglobin induction, decrease cell adhesive properties, inflammation and hypercoagulability. In line with these findings a study by Lebensburger et al., indicated that induction of fetal haemoglobin is an essential mechanism for clinical advantageous effect of hydroxyurea treatment [12].

We indicated that HU increased MCH, MCV in patients. Harmoniously a trial by Patel et al., supported our results and revealed that treatment with HU at dose 10mg/kg/day significantly increased HbF, total haemoglobin, MCV and MCH levels [13]. In tune with these Patel et al., detected that low doses of hydroxyurea reduced the rate of painful crisis and significantly increased HbF, total haemoglobin (Hb), MCV, and MCH that is in line with our results [14].

In summary, the studies indicated that HU is an effective treatment in patients with thalassemia intermedia, and although the carcinogenic effect of long-term treatment with HU remains as a serious concern, two studies with five and 10 years follow-up duration did not find any malignancy related to HU therapy [11].

LIMITATIONS

This was not a comparative study so, we could not compare the effect of HU with other treatment methods. On the other hand, the duration of follow-up was short therefore, the long-term effect and possible adverse effects of HU were not evaluated. Moreover, the sample size was relatively small. Further comparative studies with larger series and longer follow-up duration are required to confirm the results reported here.

CONCLUSION

We divulged hydroxyurea 10 mg/kg/day for one year where it significantly increased HbF, total haemoglobin, MCV and MCH in patients with thalassemia intermedia without any remarkable adverse events, Ahva3, Iran.

ACKNOWLEDGEMENTS

This study is part of Fellowship thesis for Dr. Homayon Yousefi. We wish to thank all our colleagues in Shafa Hospital and Allied Health Sciences School, Ahvaz Jundishapur University of Medical Sciences. Financial support was provided by Ahvaz Jundishapur University of Medical Sciences.

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FINANCIAL OR OTHER COMPETING INTERESTS: As declared above.

Date of Submission: **May 06, 2015**
Date of Peer Review: **Jul 17, 2015**
Date of Acceptance: **Aug 03, 2015**
Date of Publishing: **Oct 01, 2015**