

EFFECT OF HYDROXYUREA ON THALASSEMIA MAJOR AND THALASSEMIA INTERMEDIA IN IRANIAN PATIENTS

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ABSTRACT

Background: Hydroxyurea has been used in thalassemia major (T.M.) and thalassemia intermedia patients since 1994 with some success in different centers. The objective was to evaluate the effect and possible side effects of hydroxyurea in these patients.

Methodology: This was a descriptive study done in 2007 after nine years of initiation of Hydroxyurea. Medical records of 1050 patients were reviewed. Patients who had received hydroxyurea for at least three continuous months were enrolled into the study. Clinical and laboratory data during six months before and six month after starting hydroxyurea were compared.

Results: Two hundred ninety seven patients were enrolled of these two hundred forty eight (83.8%) were thalassemia major and forty eight (16.2%) were thalassemia intermedia. Dose of hydroxyurea was 15.5 ± 6.4 mg/kg /day and duration was 5.2 ± 2 years (ranging 0.5-9 years). Transfusions were completely stopped in one hundred eleven (44.7%) of thalassemia major patients with a mean Hb of 10g/dl. After 22.5 ± 18 months, using Desferal was stopped in sixty six (26.6%) patients. The reasons for stopping hydroxiurea were "ineffectiveness" in 20%, "poor compliance" in 12.4% and side effects in 13.4% of patients. The side effects were nausea, palpitation, transient leucopenia and transient raising of creatinin.

Conclusion: Hydroxyurea is effective and safe in thalassemia major and thalassemia intermedia patients and saves them from side effects of blood transfusions.

KEY WORDS: Thalassemia major, Thalassemia intermedia, Hydroxyurea, Iran.

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INTRODUCTION

Conventional therapeutic management of thalassemia major (TM) is cumbersome, costly and has side effects.¹ "Hb.F" inducing chemical agents which are being used in thalassemic

patients include: 5-azacytidin, erythropoietin, butyrate analogues, short chain fatty acids and hydroxurea.²⁻⁵ Most of these agents did not become popular mainly because of toxicity and/or poor practicability. Hydroxyurea (HU) has been used in TM and thalassemia intermedia (TI) patients since 1994⁶ and with some degrees of success in different centers.⁷⁻⁹ The beneficial effect of HU in regression of extramedullary haemopoiesis in TM patients has been increasingly reported.¹⁰⁻¹³ We report our experience with HU during last nine years in Iran.

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METHODOLOGY

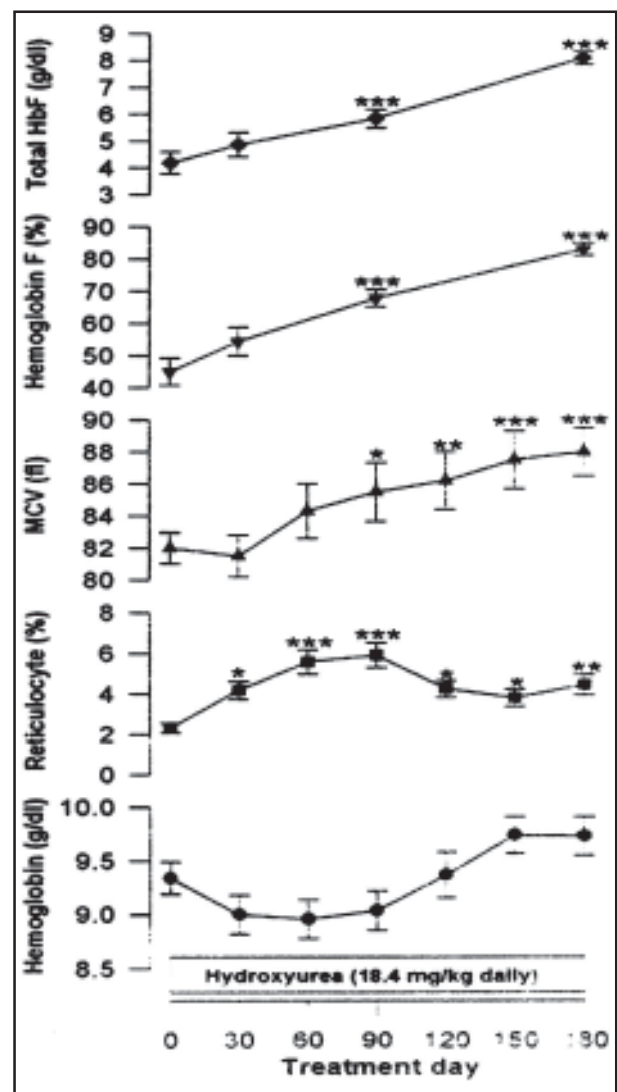
In December 2007 the medical records of all 1050 Thallasemia patients were reviewed. Patients, who had received HU for at least three continuous months, were enrolled in the study. HU had been tried on 297 TM and TI patients from June 1998 to the time of this study. TM and TI patients were defined according to Hb electrophoresis and dependency to transfusion. The patients who were on regular blood transfusion prior to HU treatment were labeled TM whereas patients who were not transfused at all or rarely transfused during their life were called TI. In 1998 the study was an open before-after clinical trial that was accepted by the ethical committee of the university and an informed consent form was signed by the patients or their parents/ guardians.

By definition, "Excellent responders" were patients on regular blood transfusions who did not need transfusion after HU, "Good response" was defined as decreasing blood demand of the patients, and "Poor response" was defined as no decline in the amount of needed transfusions. HU as 500 mg capsules (Syrea®, Medac, made in Germany) was started 10 mg/kg/ day and increased if applicable. The patients were monitored clinically and paraclinically (CBC, urea, creatinin were measured every month in first year of treatment and every three months afterward). The WBC count $<3500/\text{mm}^3$ was considered leukopenia and raised urea and creatinin >1.5 times of normal values were considered abnormal and HU would be discontinued in such situations. The drug would be started again after normalization of the tests at a lower dose and would be increased if applicable. If Hb was $<8\text{g/dl}$ blood transfusion would be offered. Side effects of treatment and reasons for discontinuation of HU were reported. The data were analysed using SPSS 13 and appropriate statistical tests. $P<0.05$ was reported as statistically significant.

RESULTS

In June 1998 the trial was started with thirty patients summary of the results is shown in Table-I. From 1998 to Dec 2007 HU was tried

on 297 patients and in 2007, two hundred patients (67.3%) of primary sample were currently on HU. Two hundred and forty eight patients (83.8%) had regular blood transfusions prior to the trial(TM) patients and 49(16.2%) were TI. One hundred fifty three patients (52%) were male. The age at diagnosis, first transfusion for (TM), starting HU and finally the age at time of the study were 5.3 ± 6.2 , 6.2 ± 6.9 , 17.5 ± 7.8 and 23 ± 8.8 years respectively. The mean dose of HU was 15.5 ± 6.4 mg/kg / day and duration of using the drug was 7.46 ± 1.62 years (ranging 0.5-9.5 years).



* $P<0.05$ ** $P<0.01$ *** $P<0.001$

Fig-1: Hb., Retic., MCV, Hb.F changes duo to HU administration in 30 TM and TI patients, 1998, Iran.

Excellent response was detected in one hundred eleven (44.7%) of TM patients with the mean Hb of 10g/dl. The remaining needed transfusions less than the primary dose before starting HU. The changes in HU and Hct before and after HU were statistically significant ($p < .0001$) [Fig-1]. The age at diagnosis of 4.5 years ($P < 0.01$) (OD 1.94, CI 95% 1.14-3.31), and the age at first blood transfusion of 5.5 years ($P < 0.03$) (OD 1.6, CI 95% 1.02-2.69) were predictors of excellent response to HU. There was no correlation between patient's gender and clinical response.

In some patients HU was discontinued; The reasons for that were "Poor response" in sixty (20%), side effects were observed in forty (13.4%) and "poor compliance" in thirty seven (12.4%) patients. Side effects were nausea in three patients (1%) and palpitation in nine (3%); also eighteen (6%) cases developed transient leukopenia, eleven (2-30 months) months after starting HU and ten (3.4%) cases developed transient renal side effect mainly triggered by pyelonephritis. These side effects occurred 1-4 (average 2.2) years after starting HU. One patient developed both leucopenia and raised blood urea. One patient became pregnant and stopped medication. There was no permanent discontinuation of the drug because of the side effects. Only twelve years old TM girl entered the trial because of increased demand for blood but after two months it turned out that she had CML; she did not respond to treatment and expired several months later. During the period, 1998 to 2005, no other fatality was noted in the group. Two patients after 2-3 years of successful treatment, (Hb as high as 12.7g/dl for months developed severe anemia (Hb. of 4g/dl) apparently after flu like symptoms. After few blood transfusions they became off blood again. Fortunately most of the patients had positive attitude toward the drug and experienced a sense of wellbeing and increased stamina and even they wished to continue HU while they were offered a blood transfusion.

The dose of Desferriexamine was reduced in patients who stopped blood transfusion and eventually discontinued after 22.5 ± 18 months

Table-I: Effect of HU administration in 228 TM & TI patients, 1998-2007, Iran.

	Before	After
Hct.	26.7 \pm 3.56	28.2 \pm 3.38*
Blood transfusion times in 6 months	4.7 \pm 3.18	1.95 \pm 2.57*
MCV(fl)	--	82.4 \pm 9.77

* $P < 0.0001$

in 66 patients. The average serum ferritin level in them was 1000ng/ml. Zinc sulfate was prescribed for the patients when they were using Desferriexamine but were off blood transfusions. Other complications of thalassemia including hypoparathyroidism in seventy seven (26%) patients, hypothyroidism in sixteen (5.4%), cardiomyopathy in thirteen (4.4%) and diabetes mellitus in eight (3%) were detected and managed appropriately. About 6% of patients had hepatitis C infection.

At the time of study 27% of patients were using sex steroids and 84% were taking folic acid supplement. About 160 patients (54%) were splenectomized; one hundred thirty one (82%) before and twenty nine (18%) after starting HU. There was no significant change in the Hct and number of blood transfusions after splenectomy in this group of patients. Our HU experience consists of 1700 patient/year. Assuming a minimum of 24 units of blood for each patient per year for TM patients; by using HU at least 33600 units of blood have been saved.

DISCUSSION

This study showed that HU was very effective in at least 44.6% of our transfusion dependent patients who tried it. In the remaining however, less blood was needed after HU. In TI the beneficial effect is not as dramatic as TM but because of decreasing the ineffective erythropoiesis, the drug theoretically could prevent bone marrow hyperplasia, disfigurement and extramedullary hematopoiesis (EH). There are reports of treatment of TI patients with neurological symptoms due to EH masses¹⁰⁻¹³ and recently we have reported eight cases of such

patients. In another historical cohort study we showed that TI patients who were using HU have statistically less significant incidence of gall stones.¹⁴ However the sense of wellbeing and increased stamina are subjective findings, which are limitations of our study.

Exact mechanism of HU in inducing Hb F has not been completely defined. It has been suggested that HU stabilizes mRNA for α chain synthesis; consequently Hb.F will be synthesized in RBC and more mature RBCs will be produced by bone marrow; in other word, HU decrease ineffective erythropoiesis.^{3-5-15,16}

In our previous report [in farsi] it has been shown that HU was successfully stabilized Hb level in 22 (73.7%) out of 30 thalassemic patients, at 9.7g/dl without transfusions. However, Hb changes were not statistically significant. In that study we also showed that total amount and percentage of fetal hemoglobin changed significantly ($P < 0.001$).

Because of different genetic backgrounds of beta thalassemia, regarding different types of beta gene mutations, Xmn1 polymorphism and the coinheritance of thalassemia deletion / excess, different clinical presentations and response to "Hb.F inducing agents" is anticipated. It has been shown that the most prevalent beta mutation in the northern parts of Iran is IVSII-1 which is a beta zero mutation.¹⁷ Akbari et al studied fifty TI patients by Restriction Fragment length Polymorphism (RFLP) method and looked for -158(C/T) mutation in promoter area of the gene and found out that 76% had either +/- or +/+ for Xmn1 limiting enzyme polymorphism. They also found out that in 60% of cases the beta gene mutation was IVSII-1. About 96% of the patients with IVSII-1 mutation had the Xmn1 marker concurrently. Examination of patients to assess both molecular determinants showed that there is physical linkage between the Xmn1 marker and the IVSII-1 allele at least in 72% of the cases who carried the two mutations.

It was previously postulated that the coexistence of the Xmn1 marker and some severe beta globin allele in cis situation under the condition of hematopoietic stress might contribute to overproduction of Hb.F causing high per-

sistence fetal hemoglobin (HPFH). It seems this phenomenon carries mild features of intermedia in a large number of Iranian TI Patients.¹⁸

Kosaryan et al studied ten families with both TM and TI in them. They revealed that in siblings with different disease severity and response to HU, the Xmn1 markers were identical in all.¹⁹ Bradai et al recently reported that beta thalassemia major or intermediate patients with XMN1 polymorphism of +/- showed better response to HU.²¹ They also reported that 90% of TI and 44.5% of TM patients had good response (transfusion need < 70% of requirement before HU). They also found that higher age at first transfusion, higher pre HU Hb, history of splenectomy and Codon6 (-A) mutation were related to better response.²⁰

So the main reason for milder anemia and different response to HU is not clear yet. Kosaryan et al in another study compared thalassemic patients on HU with those on conventional treatment and demonstrated some beneficial effect on bone mineral density of TI patients who were on HU.²¹ So continuous use of this drug might have some prophylactic effects against osteoporosis.

There was a concern regarding prolonged exposure of organs to Hb.F which has a high oxygen affinity. Rashidy et al studied forty TM and TI patients in our group, clinically, by echocardiogram in 2003, the mean age of the patients was 21±4 years, and they were using HU for 1-5 years and had no blood transfusions for long period of time. The study showed a normal systolic function in all cases and a mild diastolic dysfunction in 35% of them. So the authors concluded that using HU has no cardiac side effect associated with long term, and because HU spares body from iron overload, it is an acceptable treatment.²² There are still some concerns about possible carcinogenic effects of HU associated with long term therapy. The experience of HU for sickle cell anemia is back. Studies by Platt et al in 1984, Dover et al in 1986 and Charache et al in 1987² have showed that after more than 20 years of experience with this therapy there is no report of such side effects.

CONCLUSION

HU is a safe medication in thalassemic patients. Saving in blood transfusion costs and disease complications is remarkable. Relatively mild and transient side effects are tolerable, yet patients are to be supervised periodically and when they are anemic there must be immediate access to the hospital. The authors strongly support trial of HU in TM and IT patients.

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