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Original Research Paper

Study of efficacy of hydroxyurea in transfusion dependent B-Haemoglobinopathies

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ABSTRACT:
Introduction: Beta thalassaemia Major prevents the creation of a functioning β chain. The clinical manifestations of beta thalassaemia major include severe anaemia, stunted growth, and deformities of the skeleton within the first two years of life. The risk of transfusion-transmitted viral infections and the limited availability of blood have prompted the search for alternate methods of managing beta-thalassemia. Present study was undertaken to study effectiveness, safety profile, side effect of hydroxyurea in the treatment of children diagnosed with Beta thalassemia major.
Materials and Methods: 50 beta thalassemia major patients were enrolled & divided randomly into two groups as Hydroxyurea (HU) n=25 & placebo group n=25. Hydroxyurea (HU) group patients were given hydroxyurea 10-20 mg/kg/day (To nearest 250 mg capsule). Complete hemogram including Haemoglobin (gm/dl), RBC (millions/dl). MCV (fl), MCH (pg) & Haematocrit (%) along with serum ferritin levels, urea & creatinine were evaluated at the time of enrolment and then repeated after 6 months.
Observations and Results: At Enrolment mean ± SD of Hb (gm/dl) was 8.11 ± 1.95 in HU group & 7.85 ± 1.13 in placebo group. After 6 Month it was 9.32 ±1.86 in HU group & 8.12 ± 0.94 in placebo group. Result showed statistically significant difference in all parameters (Hb, RBC, MCV, MCH, Hematocrit, Serum Ferritin, Urea & Creatinine) in HU group.
Conclusion: In conclusion, certain transfusion-dependent β-thalassemia patients may feel better after taking hydroxyurea, which is prescribed to them to reduce their transfusion needs.

Keywords: HU, placebo, B-Haemoglobinopathies

INTRODUCTION:

Patients with thalassaemia, a hemoglobinopathy, produce aberrant red blood cells due to a deficiency in either the alpha or beta globin chains. The faulty chain of the haemoglobin molecule is used to categorise thalassaemia. One gene on chromosome 11 encodes the beta globin chain, while two nearly related genes on chromosome 16 encode the alpha globin chain. Because a normal person has two copies of their chromosomes, they have two loci that encode the beta chain and four loci that encode the alpha chain. The development of thalassaemia is highly likely to occur when any one locus is deleted[1]. Mutations in the chromosome 11 HBB gene result in beta thalassaemia, an autosomal, recessive condition. The presence or absence of mutations in one or both alleles, as well as the type of mutation, determine how severe the disease is. There are three types of beta thalassaemia: major, intermediate, and minor. Beta thalassaemia Major prevents the creation of a functioning β chain, which means that haemoglobin A cannot be built; Intermedia produces some haemoglobin A; and Minor has a mutation in one of the two β globin alleles, which means that β chain production is not significantly impaired and patients may not exhibit any symptoms[2]. The clinical manifestations of beta thalassaemia major include severe anaemia, stunted growth, and deformities of the skeleton within the first two years of life. Children that are impacted are treated with frequent blood transfusions. Transfusion requires a confirmed laboratory diagnosis of thalassaemia major and haemoglobin levels below 7 gm/dL. Iron overload occurs in patients who receive blood transfusions often[3]. To stop internal organ damage, iron chelation using deferoxamine and deferiprone is required. One medical

treatment that circumvents the problems associated with iron excess is iron chelation. Deferoxamine and other iron chelators have unpleasant and annoying side effects. Additionally, problems such as infections linked to transfusions, sensitisation, liver and endocrine disorders caused by iron overload, and iron chelator toxicities continue to increase[4]. The risk of transfusion-transmitted viral infections and the limited availability of blood have prompted the search for alternate methods of managing beta-thalassemia, particularly in a resource-poor nation like India. Previous research has extensively established the effective use of hydroxyurea in the treatment of sickle cell anaemia and thalassaemia minor. By inhibiting the ribonucleotide reductase enzyme and scavenging tyrosyl free radicals, which are involved in the reduction of nucleoside diphosphates, hydroxyurea reduces the synthesis of deoxyribonucleotides4. By raising nitric oxide levels, which trigger soluble guanylyl cyclase activation and an increase in cGMP, it raises the concentration of foetal haemoglobin (HbF) in sickle-cell disease patients. These trigger the expression of the gamma globin gene and the subsequent gamma chain synthesis required for the formation of foetal haemoglobin (HbF). Additionally, hydroxyurea inhibits the bone marrow's granulocyte production, which has a minor immunosuppressive impact, especially at vascular locations where cells have blocked blood flow[5,6]. Even if this agent's effectiveness in treating patients with beta-thalassemia major is limited, it still has to be tested to see whether it can lower the need for transfusions in these patients. Present study was undertaken to study effectiveness, safety profile, side effect of hydroxyurea in the treatment of children diagnosed with Beta thalassemia major.

MATERIAL AND METHODS:

The current study was carried out between 2022 and 2023 and is cross-sectional in nature. Permission from the institutional ethics committee was obtained before the study started. Fifty individuals with beta thalassaemia major who met the inclusion and exclusion criteria were enrolled. Every participant received an explanation of the study, and their written informed consent was acquired.

Objectives:

To assess efficacy of Hydroxyurea (HU) on clinical and hematological parameters in Beta thalassemia major patients.

Inclusion Criteria:

50 beta thalassemia major patients diagnosed on High Performance Liquid Chromatography (HPLC) and Haemoglobin Electrophoresis were enrolled.

Exclusion Criteria.

1. Patients with other hemoglobinopathies & with inconclusive HPLC reports.
2. Patients not willing to participate.

Procedure:

A detailed history including age of presentation, gender & family history was recorded at the time of enrolment. Patients were examined for clinical findings like pallor, icterus and hepatosplenomegaly. Complete hemogram including Haemoglobin (gm/dl), RBC (millions/dl). MCV (fl), MCH (pg) & Haematocrit (%) along with serum ferritin levels, urea & creatinine were evaluated at the time of enrolment and then repeated after 6 months. Haematological analysis was performed using a venous blood sample treated with EDTA. Blood samples were kept between 4 and 80 degrees Celsius, and within a week, they were examined in batches using the automated Bio Rad Variant II, β thalassaemia short program. The device provides HPLC patterns with retention periods and absorption peaks. The percentage of the fraction discovered is indicated by the area under the absorption peak. Throughout the follow-up period, patients received chelation therapy in addition to routine blood transfusions. A blood transfusion was stopped for the next week and the patient was contacted for a follow-up if the pre-transfusion haemoglobin level was found to be higher than 10.0 gm/dL during the visit. Total 50 patients were divided randomly into two groups as Hydroxyurea (HU) n=25 & placebo group n=25. Hydroxyurea (HU) group patients were given hydroxyurea 10-20 mg/kg/day (To nearest 250 mg capsule). They were examined every two weeks clinically for any sign of new onset. At the end of 6 months patients were evaluated for clinical and laboratory response.

Statistical analysis:

SPSS software, version 20, was used to conduct the statistical analysis. The data were presented as frequency in percentages N (%) and mean ± SD. Data were statistically evaluated using the unpaired-t test. If the P value was less than 0.05, statistical significance was presumed.

OBSERVATION AND RESULT:

Table 1: Clinical history

Sr No	Parameter	HU Group 25 (50 %)	Placebo group 25 (50 %)	Total 50 (100 %)
1	**Age (Mean ± SD)**	7.84 ± 3.47	8.58 ± 3.41	-
2	**Gender**			
	Male cases n (%)	8 (16 %)	10 (20 %)	**18 (36 %)**
	Female cases n (%)	17 (34 %)	15 (30 %)	**32 (64 %)**
3	**Family history n (%)**	22 (46 %)	23 (46 %)	**45 (90 %)**
4	**Pallor n (%)**	25 (100 %)	25 (100 %)	**50 (100 %)**
5	**Jaundice n (%)**	23 (46 %)	21 (42 %)	**44 (100 %)**
6	**Hepatomegaly n (%)**	25 (100 %)	25 (100 %)	**50 (100 %)**
7	**Splenomegaly n (%)**	25 (100 %)	25 (100 %)	**50 (100 %)**

Mean ± SD of age was 7.84 ± 3.47 in HU group & 8.58 ± 3.41 in placebo group. Male cases were 18 (36 %) & female cases were 32 (64 %). Pallor was found in all 25 (100 %) cases in HU group as well as in placebo group. Jaundice was found in 23 (46 %) cases in HU group & 21 (42 %) cases in placebo group. Hepato- Splenomegaly was found in all 25 (100 %) cases in HU group as well as in placebo group (Table 1)

Table 2: Blood investigation parameters

Sr No	Parameter	HU Group		Placebo group		P value
		At Enrollment	After 6 Month	At Enrollment	After 6 Month	
1	**Hb (gm/dl)**	8.11 ± 1.95	9.32 ±1.86	7.85 ± 1.13	8.12 ± 0.94	**HU: 0.029 (S) Placebo: 0.36 (NS)**
2	**RBC (million/dl)**	2.98 ± 0.55	4.26 ± 0.86	3.16 ± 0.55	3.46 ± 0.61	**HU: <0.0001 (S) Placebo: 0.07 (NS)**
3	**MCV (fl)**	77.92 ± 10.8	86.44 ± 9.74	79.36 ± 9.44	87.64 ± 5.007	**HU: 0.0052 (S) Placebo: 0.0003 (S)**
4	**MCH (pg)**	29.13 ± 3.13	32.76 ± 3.68	28.79 ± 2.84	29.21 ± 2.64	**HU: 0.0005 (S) Placebo: 0.59 (NS)**
5	**Haematocrit (%)**	38.48 ± 6.38	42.16 ± 6.38	32.12 ± 6.79	34.08 ± 7.96	**HU: 0.046 (S) Placebo: 0.3536 (NS)**
6	**Serum Ferritin (ng/ml)**	233.96 ± 58.72	153. 24 ± 88.47	231.92 ± 71.79	245.6 ± 65.77	**HU: 0.0004 (S) Placebo: 0.48 (NS)**
7	**Urea (mg/dl)**	16.04 ± 7.06	16.36 ± 6.49	18.16 ± 7.11	18.64 ± 6.98	**HU: 0.8682 (NS) Placebo: 0.81 (NS)**
8	**Creatinine (mg/dl)**	1.004 ± 0.35	0.712 ± 0.34	0.86 ± 0.33	0.91 ± 0.33	**HU: 0.004 (S) Placebo: 0.59 (NS)**

At Enrolment mean ± SD of Hb (gm/dl) was 8.11 ± 1.95 in HU group & 7.85 ± 1.13 in placebo group. After 6 Month it was 9.32 ±1.86 in HU group & 8.12 ± 0.94 in placebo group. At Enrolment mean ± SD of RBC (million/dl) was 2.98 ± 0.55 in HU group & 3.16 ± 0.55 in placebo group. After 6 Month it was 4.26 ± 0.86 in HU group & 3.46 ± 0.61 in placebo group. At Enrolment mean ± SD of MCV (fl) was 77.92 ± 10.8 in HU group & 79.36 ± 9.44 in placebo group. After 6 Month it was 86.44 ± 9.74 in HU group & 87.64 ± 5.007 in placebo group. At Enrolment mean ± SD of MCH (pg) was 29.13 ± 3.13 in HU group & 28.79 ± 2.84 in placebo group. After 6 Month it was 32.76 ± 3.68 in HU group & 29.21 ± 2.64 in placebo group. At Enrolment mean ± SD of Haematocrit (%) was 38.48 ± 6.38 in HU group & 32.12 ± 6.79 in placebo group. After 6 Month it was 42.16 ± 6.38 in HU group & 34.08 ± 7.96 in placebo group. At Enrolment mean ± SD of Serum Ferritin (ng/ml) was 233.96 ± 58.72 in HU group & 231.92 ± 71.79 in placebo group. After 6 Month it was 153. 24 ± 88.47 in HU group & 245.6 ± 65.77 in placebo group. At Enrolment mean ± SD of Urea (mg/dl) was 16.04 ± 7.06 in HU group & 18.16 ± 7.11 in placebo group. After 6 Month it was 16.36 ± 6.49 in HU group & 18.64 ± 6.98 in placebo group. At Enrolment mean ± SD of Creatinine (mg/dl) was 1.004 ± 0.35 in HU group & 0.86 ± 0.33 in placebo group. After 6 Month it was 0.712 ± 0.34 in HU group & 0.91 ± 0.33 in placebo group.

Result showed statistically significant difference in all parameters (Hb, RBC, MCV, MCH, Hematocrit, Serum Ferritin, Urea & Creatinine) in HU group (Table 2).

DISCUSSION:

In present study mean ± SD of age was 7.84 ± 3.47 in HU group & 8.58 ± 3.41 in placebo group. Male cases were 18 (36 %) & female cases were 32 (64 %). In similar study Farhad Zamani et al (2009)[7] found the mean age of the patients was 18.38 years (range: 10 – 40 years). Yadav A et al (2016)[8] in their study found the mean age ± SD of the subjects at the time of enrolment in the study was 11.7 ± 3.95 years. Out of twenty-five patients, 17 (68%) were male and 8 (32%) female.

In present study at Enrolment mean ± SD of Hb (gm/dl) was 8.11 ± 1.95 in HU group & 7.85 ± 1.13 in placebo group. After 6 Month it was 9.32 ±1.86 in HU group & 8.12 ± 0.94 in placebo group. At Enrolment mean ± SD of RBC (million/dl) was 2.98 ± 0.55 in HU group & 3.16 ± 0.55 in placebo group. After 6 Month it was 4.26 ± 0.86 in HU group & 3.46 ± 0.61 in placebo group. At Enrolment mean ± SD of Haematocrit (%) was 38.48 ± 6.38 in HU group & 32.12 ± 6.79 in placebo group. After 6 Month it was 42.16 ± 6.38 in HU group & 34.08 ± 7.96 in placebo group. In similar study Azamsadat Hashemi et al (2009)[9] found mean haemoglobin level increased from 8.9 to 9 g/dl (P-value=0.796), mean red blood cell (RBC) count increased from 3.54 to 3.64 million/dl (P-value=0.56), mean corpuscular volume (MCV) decreased from 78.6 to 77.2 fl (P-value=0.325), mean corpuscular hemoglobin (MCH) decreased from 25.19 to 25.9 pg. Yadav A et al (2016)[8] in their study found consistent and progressive increase in the hemoglobin was observed throughout the study after 6 months of therapy ($p < 0.05$).

Previous studies have demonstrated that if given for at least three to six months, three classes of inducing hypomethylating drugs, including HU, decitabine, and 5-azacytidine, can raise total Hb levels by 1 to 5 g/dL above baseline10. The therapeutic response to HU is influenced by a variety of factors, including as XmnI polymorphism, α and γ globin chains, genetic alterations, and other biochemical parameters.

Limitations:

Limitations of present study is it was relatively short study period to assess the long-term safety and efficacy of the drug. Also sample size is short for coming to any definite conclusion.

CONCLUSION:

In conclusion, certain transfusion-dependent β-thalassemia patients may feel better after taking hydroxyurea, which is prescribed to them to reduce their transfusion needs. Therefore, it is advised that patients with thalassaemia major use hydroxyurea to reduce or perhaps eliminate the need for frequent transfusions and the associated iron excess during treatment.

Conflict of Interest:

The authors declare that there is no conflict of interest.

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