International Journal of Pharmacology and Clinical Research

ISSN Print: 2664-7613
ISSN Online: 2664-7621
Impact Factor: (RJIF) 8.29
IJPCR 2025; 7(2): 527-534
www.pharmacologyjournal.in
Received: 08-08-2025
Accepted: 13-09-2025

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Emerging role of hydroxyurea in the clinical management of thalassemia

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DOI: https://www.doi.org/10.33545/26647613.2025.v7.i2g.148

Abstract
Thalassemia is a genetic hemoglobin malady that causes inefficient erythropoiesis and chronic anaemia, which were conventionally treated with a regular blood transfusion and iron chelation therapy. By causing fetal hemoglobin (HgF) synthesis, hydroxyurea assists patients with specific cases of hemoglobinopathy in improving hemoglobin levels, suppressing hemolysis, and decreasing the number of transfusion. Clinical trials have shown unpredictable yet encouraging outcomes especially in thalassemia intermedia where it improves the erythropoietic efficiency and alleviates the complications of iron overload. Hydroxyurea is a cost-effective, available treatment with potential to be used in resource-limited regions although its long-term effectiveness and safety have to be examined further. Issues of monitoring of treatment, variability of response and selection of the patient are also a major consideration. This review outlines the possible therapeutic value of hydroxyurea, based on the value of the drug to maximize the disease control and enhance the quality of life among thalassemia patients.

Keywords: Hydroxyurea, thalassemia, fetal hemoglobin, transfusion reduction, hemoglobinopathy, disease management

Introduction
The thalassemias are inherited, autosomal recessive disorders of hemoglobin (Hb) synthesis characterized by a variety of molecular defects and are among the most common genetic diseases worldwide. The principal forms, α- and β-thalassemia, result from mutations in globin genes that lead to a deficit or qualitative change in the production of the α-globin and β-globin chains of adult Hb, respectively [1].

In 1925, thalassemia was first recognized in its severe (named Cooley's anemia) and milder forms independently in the US and Italy, which are today known as thalassemia major (TM) and thalassemia intermedia (TI) [2]. Patients with thalassemia do not produce enough hemoglobin (Hb) A (α2β2) because their cells cannot manufacture either the alpha or beta polypeptide chain of human hemoglobin [3]. TH usually results in the underproduction of normal globin proteins, often through mutations in regulatory genes. Four protein chains, two α- and two β-globin chains organized in a heterotetrameric configuration, make up normal hemoglobin. Unlike sickle-cell disease, which results in a specific mutant type of β-globin, TH individuals produce a deficit of either α- or β-globin. The hemoglobin molecule's damaged chain is used to categorize TH patients. The α-globin chain is affected in α-TH, whereas the β- globin chain is affected in β-TH [4].

Classification of thalassemia alpha thalassemia
There are several forms of alpha thalassemia. The most common forms are: Silent carrier alpha thalassemia: There are two alpha genes located on each chromosome 16. In the silent carrier state, one of the alpha genes is absent, leaving three of four genes. Alpha thalassemia trait: This form is usually caused by the deletion of two alpha (a) genes on one chromosome 16 or the deletion of one gene from each chromosome 16.

Beta thalassemia
In contrast to the duplication found in alpha thalassemia, there is only one beta-globin gene on chromosome 11.

There are several forms of beta thalassemia: Silent carrier beta thalassemia or beta thalassemia minor: The mutation that causes this form of thalassemia is very mild. These patients usually have no signs or symptoms, or have some minor changes in number or size of the red blood cell. This is the most common form of beta thalassemia [3].

β-thalassemia is highly prevalent, with 80 to 90 million people reported to be carriers across the world (1.5% of the global population). It includes three main forms: β-thalassemia major (TM), also referred to as "Cooley's anemia" and "Mediterranean anemia"; β-thalassemia intermedia (TI); and thalassemia minor, called "β-thalassemia carrier," "β-thalassemia trait," or "heterozygous β-thalassemia [5]. Thalassemia major is characterized by severe anemia, and survival depends on regular blood transfusion, with an unavoidable iron overload resulting in multiorgan damage due to free radical generation [6]. The phenotype of TI may also result from the increased production of α-globin chains by a triplicated or quadruplicated α-genotype associated with β-heterozygosity. In TI, the genetic basis for phenotypic diversity is best explained in terms of primary, secondary, and tertiary genetic modifiers [7].

Patients with thalassemia minor (TM) are often asymptomatic. Thalassemia can be sub grouped to transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT). Phenotype of NTDT includes heterogeneous thalassemia genotypes that do not require frequent transfusions but is more severe than TM and have several complications due to ineffective erythropoiesis, extramedullary hematopoiesis and iron overload. Five form of NTDT has been described:

Beta thalassemia intermedia, hemoglobin E β-thalassemia, HbH disease, hemoglobin S β- thalassemia and hemoglobin C β thalassemia [8].

Epidemiology

This disorder has been found to be highly prevalent in tropical and sub-tropical regions of the world (e.g., Southeast Asia, the Mediterranean area, the Indian subcontinent, and Africa), where the estimated prevalence rates are 12-50% in the case of alpha thalassemia and 1-20% in that of beta thalassemia [9, 10]. It is historically known that thalassemia is most prevalent in African, Asian, and Mediterranean countries, reflecting an evolutionary development of genetic selection processes that are protective against malaria [11].

A precise estimation of the prevalence and incidence rates of thalassemia is required for the effective management of patients, development of prenatal diagnostic strategies, and utilization of healthcare resources [12].

The average prevalence of β thalassemia carriers is 3-4% which translates to 35 to 45 million carriers in our multi-ethnic and culturally and linguistically diverse population of 1.21 billion people which also includes around 8% of tribal groups according to the Census of India 2011. Several ethnic groups have a much higher prevalence (4-17%) [13, 14].

Etiology

Thalassemia is autosomal recessive, which means both the parents must be affected with or carriers for the disease to transfer it to the next generation. It is caused by mutations or deletions of the Hb genes, resulting in underproduction or absence of alpha or beta chains. There are over 200 mutations identified as the culprits for causing thalassemias. Alpha thalassemia is caused by deletions of alpha-globin genes, and beta thalassemias are caused by a point mutation in splice site and promoter regions of the beta-globin gene on chromosome 11 [15].

Pathophysiology

Haemoglobin is a tetramer, made up of 4 identical protomers 2 to 2. Each protomer is composed of a globin (alpha or beta chain of globular glycoproteins) and heme which carrying an iron atom [16].Haemoglobin synthesis is controlled by two multigene clusters, on chromosome 16 (is composed of 3 homologous genes, the zeta(ζ)gene, alpha 1 (HBA1) and alpha 2 genes (HBA2))and on chromosome 11 containing five functional genes, (ε (HBE), Gγ (HBG2), Aγ (HBG1), δ (HBD), and β (HBB)), which are arranged along the chromosome in the order of their developmental expression to produce different Hbtetramers sequentially at each stage of embryonic and fetal development: Embryonic (Hb Gower-1 (ζ2ε2), Hb Gower-2 (α2ε2) and Hb Portland (ζ2β2)), fetal (α2γ2) and adult (HbA, α2β2and HbA2, α2δ2) [17].

Upstream of the entire βglobin complex is the locus control region (LCR), which consists of five DNAse hypersensitive (HS) sites (designated HS 1-5). The LCR plays a critical role in gene expression by maintaining an open chromatin state and acting as a powerful enhancer of globin gene transcription; in its absence, the level of βglobin gene expression is low. Four of the sites (HS 1erythroid-specific, encompassing binsequences for erythroid-restricted transcription factors (GATA-1 and NF-E2), while HS5 is ubiquitous [18]. In β -thalassaemia major the excess unpaired and insoluble α globin chains precipitate at the red cell precursors membrane and Free iron catalyses the formation of reactive oxygen species leading to oxidative cell damage and premature cell death by apoptosis. This happens within the erythropoietic tissue and so results in ineffective erythropoiesis (IE) and haemolysis of mature red cells [19].

Clinical manifestations

Classically, individuals with severe β-thalassemia have presented with variable but often very severe degrees of anemia, expansion of the bone marrow spaces secondary to erythroid hyperplasia, hepatosplenomegaly, and extramedullary hematopoiesis in the chest and abdomen [20, 21]. Iron overload have come to dominate the clinical phenotype of individuals with severe β-thalassemia. Cardiac dysfunction is the main clinical problem that may lead to early death. Endocrine abnormalities, particularly hypogonadism, low growth hormone, hypothyroidism, and diabetes mellitus, are also significant problems [22]. Cardiac manifestations of thalassemia include arrhythmias, both atrial and ventricular, and/or congestive heart failure [23]. Endocrine Abnormalities include growth retardation secondary in part to growth hormone deficiency and hypogonadism are typically the initial manifestations of iron overload in β-thalassemic patients [24]. Osteoporosis often occurs in patients with thalassemia, reflecting marrow expansion, endocrine deficiencies, iron toxicity, and the potential toxicity of chelators [25].

Diagnosis

Iron Studies Normal or slightly increased ferritin levels are present in thalassemia. Transferrin levels are almost normal in thalassemia as compared to iron deficiency anemia [26].

Peripheral Smear
Peripheral smear shows microcytic hypochromic anemia with target cells, teardrops, and cells with basophilic stipplings [26].

Haematologic and biochemical: The typical findings of RBC indices show reduced haemoglobin (30-70 g/l), haematocrit, red blood cell count, mean corpuscular volume (MCV) (50-60 fL), mean Corpuscular Haemoglobin (MCH) (12-18pg), raised biliribune and LDH. The iron deficiency (iron content) and the iron stores represented by ferritinemia are greatly increased [27].

Haemoglobin Analysis: Diagnosis of β-thalassaemia is confirmed by qualitative and quantitative Hb analysis, either by high-performance liquid chromatography or capillary electrophoresis [28]. Hb analysis is needed to determine α- and β-thalassemia carriers and disease. Automatic HPLC and CE system are sensitive and precise methods for qualitative and quantitative analyses of Hb components in red blood cells [29].

Molecular analysis for alpha and beta thalassemic mutations
Allele Specific PCR
This technique employs two primers identical in sequence except for the 3′-terminus base, one of which is complementary to the wild-type and the other for the mutant base; a common primer for the opposite strand must of course be used as well. For primer extension to occur using *Taq* polymerase which has no 3′-5′ exonuclease (proofreading) activity, perfect matching of the primer 3′-terminus with the DNA template must occur. With a normal individual, PCR product will be seen only in the reaction employing the wild-type primer set. A heterozygote will generate a band using both wild-type and mutant primer set, and an individual with homozygous mutation will be negative with the normal and positive with the mutant primer set [30].

Reverse Blot analysis
The suspected mutation can be identified by hybridization of an allele-specific oligomer (ASO) DNA probe with the PCR product which is immobilized on a membrane filter sheet as a dot. The ASO probe can be radiolabeled with 32P for autoradiography or has attached reporter groups (biotin, digoxigenin, or an enzyme such as horseradish peroxidase) which can subsequently be visualized in a chemiluminescent or colorimetric reaction.

Real time PCR with melting curve analysis
The real-time PCR or quantitative PCR (qPCR) is widely used to detect, characterize, and quantify nucleic acids. It is high throughput, automation, and low risk of post-PCR contamination.

Direct DNA sequencing
An aliquot of the amplified DNA can be subjected to another round of PCR but in the presence of a single primer strand; or the original PCR product can be denatured and rapidly cooled so that the two strands remain separated; or one of the primer strand is phosphorylated at the 5′-terminus and the PCR product treated with lambda exonuclease which digests 5′- phosphorylated strand in a dsDNA; or biotin can be incorporated into the 5′-terminus of one of the primer strand enabling the PCR product to be adsorbed onto streptavidin-coated magnetic beads, which can then be treated to denature the duplexes and allow removal of the non- biotinylated strands from the beads. [31].

Testing procedures
High-performance Liquid Chromatography
HPLC is used increasingly as the diagnostic procedure for hemoglobinopathies. Its working principle lies behind the interaction between the charges on the ion exchange material and that of the hemoglobin molecule.

Cellulose Acetate Electrophoresis
This is a simple, reliable, and rapid process where the hemoglobin undergoes electrophoresis at pH 8.4-8.6 using a cellulose acetate membrane. Its principle is that hemoglobin is a negatively charged protein at alkaline pH, and on electrophoresis, it migrates to the anode [14].

Microcolumn Chromatography
Microcolumn chromatography depends on the exchange of charged groups between the charged group of the hemoglobin molecule and charged groups on ion exchange cellulose. If a mixture of hemoglobins is adsorbed on the cellulose, particular hemoglobin would be separated from the column using a developer (buffer) at a specific pH or ionic strength [32].

Management for beta thalassemia
Without treatment, β-thalassaemia major is lethal within the first decade of life due to the complex pathophysiology. Several conventional modalities for the management of TDT and NTDT patients exist today. These include blood transfusion, splenectomy, iron chelation therapy and for some patient's haematopoietic stem-cell transplantation (HSCT) [33].
In addition to the aforementioned treatment methods for β-thalassemia, it is essential to reduce ineffective erythropoiesis and manage iron overload to optimize the alleviation of clinical symptoms and extend the patient lifespan [34].

Blood transfusion
The transfusion rehabilitation in β-thalassemia major is to maintain the level of hemoglobin in plasma and to correct anemia which is the result of endogenous erythropoiesis. Blood transfusion therapy should be started in case of severe anemia after confirmation of the diagnosis of thalassemia. Though, individuals, who have Hb > 7 g/dl, various aspects like growth retardation, increasing splenomegaly, facial changes as well as the expansion of bone, should be measured. Regular blood transmission would not be late till after the second-third year, because multiple red cell antibodies might be developed and suitable blood donors are difficult to find. Numerous transfusion treatments have been projected over the years; however, the utmost extensively conventional goal at pre-transfusion hemoglobin near to 9 to 10 g/dl as well as a post-transfusion level of hemoglobin should be 13 to 14 g/dl. This inhibits impairment of organs, retardation of growth as well as malformations of bones which might lead to normal quality and activity of life. The frequency of blood transfusion depends on numerous causes such as the level of hematocrit and Hb as well as the weight

of the patient. Blood transfusion therapy should not transfer RBCs more than 15 to 20 ml/kg daily to evade a profligate rise in the volume of blood. The efficiency of transfusion therapy should be examined via pre- and post-transfusion levels of hemoglobin as well as hematocrit because these quantities can enable to monitor of iron intake and the requirement of RBCs [35].

Splenectomy

In thalassemia major and thalassemia intermedia, overactivity of the spleen occurs as a consequence of severe hemolysis. Splenomegaly in early age may be prevented after initiation of a regular blood transfusion. However, hypersplenism can develop in children among 5-10 years of age. Splenectomy protects the patients against poor health and growth retardation by decreasing the transfusion requirement, improving the level of Hb as well as decline the accumulation of iron. Removal of the spleen is suggested when a requirement of transfusion is greater than 200 to 220 ml RBCs/kg with 70% hematocrit as well as packed RBCs 250-275 ml/kg with 60% hematocrit per year. A meningococcal and pneumococcal vaccine before surgical removal of the spleen is recommended while after splenetic antimicrobial prophylaxis with penicillin is suggested for the reduction of irresistible infections [35].

Iron chelation therapy

In the case of regular transmission of blood, each RBC contains 200 mg of iron which results in 0.3-0.6 mg/kg per day iron accumulated. Iron chelators are categorized into three classes: deferasirox (DFX), deferiprone (DFP), and deferoxamine (DFO). The removal of iron is one of the most important management for those individuals who have blood transfusion. The DFO is a derivative from Streptomyces pilosus with a half-life of 8-10 minutes and has a molecular weight of 657. It enters into parenchymal cells of the liver where it chelates the iron as the iron chelator deferoxamine in plasma and bile. The duration of dose differs from patient to patient and depends upon how much iron is overloaded after transfusion. The initial use of 1 week regularly in transfusion-dependent patients of thalassemia, the commended dosage of deferoxamine is 30-40 mg/kg daily each week and 40-50 mg/kg and consequently to 60 mg/kg in teenagers and grownups, respectively. Chelation therapy inaugurates after 20-25 RBCs units are transferred between 2 to 4 years of age. The half-life of deferiprone is 1.5-4 hours in plasma and it is absorbed by the gastrointestinal tract. The dose is recommended daily 75 mg/kg daily, administration verbally in three allocated dosages with meal times and this dose might be augmented 100 mg/kg per day. Deferiprone infiltrates cell membranes more swiftly than deferoxamine and it is capable of chelating intracellular iron. It has efficacy for improving the function of cardiac by eradicating iron from cardiac as well as preventing cardiac diseases induced by overloaded iron. Regular observation of complete blood count weekly is required as 1% of the patients treated with DFP in case of the prospective threat of agranulocytosis. The half-life of deferasirox is 12-18 hours and recommended orally once a day. The prescribed dosage is 20-30 mg/kg daily but some individuals may get assistance through increasing the dosage up to 40 mg/kg daily, it is effective both in grownups as well as offspring [35].

The introduction of iron-chelation therapy coupled with regular blood transfusion has led to improved survival in TDT patients. Three iron chelators are currently available: deferoxamine (DFO) was the first clinically approved iron chelator for treatment of β-thalassaemia and has been in regular use since the 1980s, followed by the approval of deferiprone (DFP) and deferasirox (DFX) [34]. The main differences between these 3 iron chelators are their route of administration, the dosage range, their half-life and schedule [36].

Transplantation of bone marrow

The relocation of bone marrow remains the main conclusive treatment, reachable for patients of thalassemia (Majolino *et al*., 2017). The results in young patients are 3% mortality rate and 87% thalassemia free survival. But BMT has few disadvantages such as human leukocyte antigen matched compatible donor is required for this remedial process (Sabloff *et al*., 2011). The best results with very young individuals are: rejection rate is 23%, the mortality rate is 7%, and thalassemia free survival rate is 70%. Treatment for thalassemia through bone marrow transplantation is still not available for all Indian patients (Jeengar *et al*., 2017) [35].

Hematopoietic stem cell transplant (HSCT)

HSCT remains the only curative treatment for β-thalassaemia patients without altering the person's own genome by gene therapy. Its rationale is to restore tissue's capability of producing functional Hb in TDT patients [37]. For this procedure, ideally the donor is a human leukocyte antigen-identical sibling of the patient, but since >60% of patients lack such a suitable family donor, transplants from matched unrelated donors are still possible [38]. The outcomes of HSCT in β-thalassaemia patients depends on several factors, such as iron overload, liver fibrosis and hepatosplenomegaly status. Apart from these, the outcome also depends on the patient age as survival rates is >88% if HSCT is performed during patient's childhood [39].

Even though with this greater improvement, HSCT is still a challenging procedure associated with several risks and complications with graft-vs.-host disease being the major cause of morbidity and mortality following allogenic HSCT [40].

Improving iron overload in β-thalassaemia

In β-thalassaemia, apart from anaemia, ineffective erythropoiesis iron overabsorption to support the increased iron demand for Hb synthesis. This leads to organ iron overload especially in liver, spleen, heart and pancreases, giving rise to liver cirrhosis, heart failure and diabetes [41]. Hepcidin is the master regulator of iron. It is synthesized in the liver and secreted in the bloodstream. Once in circulation, hepcidin binds to ferroportin (iron exporter) causing the hepcidin-ferroportin to be degraded by lysosomes. This process is regulated by iron demand, iron stores, erythropoiesis, hypoxia and inflammation [26]. In β-thalassaemia; anaemia, tissue hypoxia and increased erythropoietin production promotes the suppression of hepcidin. In doing so, iron absorption is increased, therefore the use of drugs/agents to stimulate hepcidin expression and activity in these patients would be beneficial [26, 42].

Efficacy of Hydroxyurea in Transfusion-Dependent Major β-Thalassemia Patients: Regular blood transfusions

lead to iron overload, resulting in organ damage and, ultimately, death of these patients [43]. Therefore, there is a need for alternative therapy to reduce the burden of blood transfusions in patients with transfusion-dependent β-thalassemia.

Hydroxyurea (or hydroxycarbamide), primarily a cytotoxic, anti-metabolic, and antineoplastic agent, also induces fetal hemoglobin (HbF) synthesis by stimulating γ-globin production. Besides stress erythropoiesis, which is considered to be the primary mechanism, production of nitric oxide and the soluble guanylyl cyclase and cyclic guanosine monophosphate-dependent protein kinase pathway gene have been proposed as being responsible for inducing γ-globin synthesis [44]. Apart from its established role in stimulating γ-globin production, hydroxyurea may also have a broader impact in enhancing globin synthesis, including β-globin, in certain patients who are able to express normal β-globin chains [45]. Therefore, hydroxyurea induces not only hemoglobin F but also overall hemoglobin production. After being identified as a potent hemoglobin inducer, hydroxyurea became one of the important therapeutic agents for the management of patients with sickle cell anemia and has been widely assessed in thalassemia intermedia, with varying results [46].

Discussion

Hydroxyurea (also known as hydroxycarbamide) is an antimetabolite S-phase-specific drug that reversibly inhibits ribonucleoside diphosphate reductase (rNDP) enzyme. This enzyme catalyses the conversion of ribonucleotides to deoxyribonucleotides which is an essential step in DNA biosynthesis. Inhibition of rNDP and impaired synthesis of DNA prevent the progression of cells from the G1 or pre-DNA synthesis phase of the cell cycle. Also, hydroxyurea is cytotoxic to S-stage cells resulting in their destruction. The enzyme inhibitory effect of hydroxyurea is limited to the de novo synthesis of DNA and DNA repair; it does not have an effect on RNA or protein synthesis. [47, 48]. Hydroxyurea is a well-tolerated oral drug that has been in use for several decades.

The most common adverse effect of hydroxyurea is cytopenia (approximately 20%) due to a dose-dependent and transient suppression of the bone marrow. Although it affects all haematological cell lineages, neutrophils are most commonly affected, resulting in mild to moderate neutropenia. Reticulocytopenia and thrombocytopenia are also reported. These haematological toxicities are reversible by withholding the drug for a few weeks or decreasing the dose [49, 50]. Another commonly reported side effect is hyperpigmentation of nails and skin, especially in palms and soles. Additionally, hydroxyurea is also known to cause headache and gastrointestinal symptoms that include nausea, vomiting, abdominal pain and constipation [51].

In addition to decreasing the transfusion requirement, hydroxyurea has shown to be effective in mitigating extramedullary haematopoiesis and ineffective erythropoiesis in patients with NTD β-thalassaemia [52, 53, 54]. Treatment with hydroxyurea is associated with a significant reduction of spleen size in several studies [55, 56]. A study among a large cohort of patients with NDT β-thalassaemia revealed that hydroxyurea reduces the risk of leg ulcers, pulmonary hypertension and osteoporosis [57]. Despite these beneficial effects, several aspects of hydroxyurea treatment in NTD β-thalassaemia that include optimal dosing and safety in children require further evaluation.

Oral hydroxyurea is easily absorbed through the gastrointestinal tract and distributed rapidly and widely in the body. The peak plasma concentration is reached 1 to 4 h after an oral dose. It is recommended to start with a lower dose of 10-15 mg/kg/day and gradually increase in steps of 2.5-5 mg/kg/day to a usual dose of 15-30 mg/kg/day (the maximum dose is 35 mg/kg/day). The effects of hydroxyurea are transient as the drug is rapidly cleared from the circulation. Elimination of hydroxyurea is mainly through urine after being metabolised in the liver [49, 51, 58].

A study conducted by Hatamleh M I *et al.,* conducted a meta-analysis determine the efficacy of hydroxyurea in patients with transfusion dependent major β-thalassemia. Outcomes assessed in the present meta-analysis included transfusion in one year and intervals between transfusions (in days). Other outcomes assessed in the present meta-analysis were fetal hemoglobin (%), hemoglobin (%), and ferritin levels (ng/dl). A Total of five studies were included in the analysis enrolling 294 patients with major B-thalassemia. The pooled analysis reported that the mean interval between transfusions was significantly higher in patients receiving hydroxyurea compared to those not receiving hydroxyurea. Hemoglobin was significantly higher in patients receiving hydroxyurea compared to its counterparts. Patients receiving hydroxyurea had significantly lower ferritin levels compared to those not receiving hydroxyurea. These findings suggest that hydroxyurea may be a promising and cost-effective alternative to blood transfusions and iron chelation therapies for beta-thalassemia patients. [59].

A study by Najjari A, Hashemi A *et al.,* 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. t. Moreover, they emphasized HU treatment is safe without remarkable adverse events in children [60, 61].

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 [62].

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. 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 [63].

Conclusion

Hydroxyurea has emerged as an emerging new therapeutic strategy in the treatment of thalassemia. In certain patients, this could result in reduced transfusion needs, and elevated hemoglobin, by enhancing fetal hemoglobin synthesis. Hydroxyurea is another possible alternative to conventional treatment methods that commonly take recourse to blood transfusions and iron chelation. Hydroxyurea is an inexpensive and acceptable option and can usually be purchased over the counter, particularly in populations where limited health care is prevalent. Research results for hydroxyurea suggest it will enhance the quality of life of the patients, through reductions in ineffective erythropoiesis and some of the issues that generate thalassemia. But understanding the long term safety and responsiveness variability is still to be achieved through continuous monitoring of both the patients and the doctors. With ongoing research investment in thalassemia treatment, the potential for curative therapy through stem cell transplant and gene therapy remains actual, Hydroxyurea provides a valuable bridging therapy for the treatment of thalassemia, until an ultimate treatment modality with convergent public health objectives is realized to maximize patients' care and outcomes.

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