DOI: https://doi.org/10.53350/pjmhs221610138

ORIGINAL ARTICLE

Impact of Hydroxyurea on Blood Transfusions and Its Safety in β-Thalassemia patients

MALIK ASIF HUSSAIN[1], AYESHA ASIF[2], USAMA GORSI[2], AAMIR MUSHATQ[3], UMAR FAROOQ GOHAR[4], ASAD IFTIKHAR SHAH[5]
[1]*Department of Pathology, University of Hail, KSA*
[2]*Riphah Institute of Pharmaceutical Sciences, Riphah International University Lahore Pakistan*
[3]*Department of Pharmaceutical Sciences, Government College University Lahore Pakistan*
[4]*Institute of Industrial Biotechnology , Government College University Lahore Pakistan*
[5]*Punjab Institute of Neurosciences Lahore General Hospital Lahore Pakistan*
Correspondence to Dr. Umar Farooq Gohar, Email: dr.mufgohar@gcu.edu.pk

ABSTRACT

Background: Thalassemia is a genetic defect characterized by abnormal hemoglobin in red blood cells and resultant anemia. Currently, regular blood transfusion or fetal hemoglobin inducers or a combination of these is clinically used to manage these patients.
Aim: To observe effectiveness of Hydroxyurea in β-Thalassemia patients, particularly focusing on change in frequency of blood transfusions.
Methods: This study analyzed data of the patients registered with thalassemia society of Pakistan and Sundas Foundation of district Lahore, Punjab, Pakistan. Eighty seven patients were selected for analysis based on available data and specific inclusion criteria. The results were calculated using "dependent/paired sample t test" and presented in form of graphs.
Results: Out of eighty seven patients, 72 % of the patients were diagnosed with thalassemia major, 26% with thalassemia intermedia and 1% with thalassemia minor. Additional analysis showed more cases in males (57 %); dominance of cases in cousin marriages (87 %) and majority of patients were 1-10 years (60 %) old. In this study, the impact of hydroxyurea was observed on reduction of blood transfusions in thalassemia patients. Overall, 11.5% patients showed excellent response, 65.5 % were good responders and 25% patients did not show clinical improvement with hydroxyurea use. The dosage of hydroxyurea was based on weight of the patients.
Conclusions: It is hence concluded that Hydroxyurea is safe and effective drug for thalassemia patients, as it reduces the blood transfusion need of the patients and help to improve their quality of life.
Keywords: Blood transfusion, Anemia, Hydroxyurea, Thalassemia.

INTRODUCTION

Thalassemia, also known as 'thal', is a blood disorder which is genetically inherited and is caused by genetic defect. Cooley's anemia and Mediterranean anemia are synonymous terms used for Thalassemia[1]. Disease is prevalent globally but in particular Thailand and Mediterranean countries have significant number of patients suffering from thalassemia. Common clinical presentation is with symptoms of anemia such as fainting, shortness of breath, fatigue and generalized weakness. Thalassemia is sometimes misdiagnosed as iron deficiency anemia until specific blood tests are carried out. In normal chains of hemoglobin, α and β polypeptide chain are in equal quantity. In thalassemia, the balance of these chains is disturbed due to defective synthesis by globin genes, which results in precipitation of excessive polypeptide chains in immature red blood cells (RBCs). This ultimately disturbs the process of erythropoiesis. Furthermore, this precipitation causes hemolysis of mature RBCs[2]. There are two common types of thalassemia; α-thalassemia and β-thalassemia. The α-thalassemia occurs during infancy or fetal life and is characterized by less, abnormal or absent α-chains, which are controlled by four genes. Adults have β-chains in excess and children have γ-chains in excess due to deficiency of α-chains. This results in hemolysis as well as ineffective erythropoiesis. In α-thalassemia, one defected gene will cause no significant effect on quality of life for the person. Presence of two defective genes is associated with mild form of anemia. Three faulty genes result in chronic anemia and treated by regular blood transfusions. The pregnancy with a fetus with four mutated genes does not survive[3]. The β-thalassemia is of four types; β-thalassemia major, β-thalassemia minor, β-thalassemia intermedia and hemoglobin E β-thalassemia. The patients suffering from β-thalassemia major require regular blood transfusions throughout their life[4].

Hemoglobin (Hb) related defects affect about 7% of the world's population, mostly as carrier states. The prevalence of β-thalassemia in Pakistan is around 1-7 %[5]. A person who carries only one abnormal Hb gene usually shows no health issues. Every year, almost 300,000–500,000 children are born with hemoglobin related disorders[6]. More than 5000 children are born with β-thalassemia major in Pakistan annually[7]. About 50,000 – 100,000 children with β-thalassemia major die annually in third world countries[8].

Hydroxyurea (HU) is an antimetabolite, cytotoxic and antineoplastic agents used in myeloproliferative diseases and human immunodeficiency viral infections. The finding of HU as an agent, which can induce HbF, made it an important drug to treat patient of sickle cell disease[9].

The production of fetal hemoglobin by hydroxyurea increases hemoglobin level which decreases blood transfusion need but its efficacy decreases with long term therapy. It is a synthetic drug which belongs to aminoketone group. Its pharmacological group is ribonucleoside diphosphate reductase on the basis of mechanism of action. It is also known as antineoplastic and antimetabolite drug[10].

Hydroxyurea reduces the phospholipids expression on both RBCs and Platelets, and minimizes RBCs attachment with thrombospodin. Hydroxyurea is nitric oxide donor and decreases hemostatic activation by reducing the white blood cell count especially monocyte count that cause expression of tissue factor[11]. It acts as potent ribonucleotide reductase inhibitor (an enzyme needed for the synthesis of DNA and its repair) and a potent fetal hemoglobin (HbF) inducer. Due to this effect, hydroxyurea has evolved as one of the significant therapeutic drug for managing β-thalassemia and sickle cell disease. A cytotoxic effect that is cell killing effect causes stress erythropoiesis with increase in HbF level. The HbF induction ability of hydroxyurea both in monkeys and anemic patients with sickle cell disease has been reported[12]. Bradai et al (2003) proposed a constant hemoglobin level after treatment with hydroxyurea and all seven patients treated with hydroxyurea in their study stopped receiving blood transfusions[13]. Hydroxyurea reduces the need of transfusions and maintain Hb level[14]. Hydroxyurea has been used in thalassemia major and thalassemia intermedia patients, however all aspects of

Received on 03-06-2022
Accepted on 13-10-2022

mechanisms of action of hydroxyurea are not fully understood yet[15].

METHODS

Samples: Patients registered with thalassemia society of Pakistan and Sunda Foundation of district Lahore, Punjab, Pakistan were included in this study. A total of 87 patients were included based on following inclusion criterion;

- Having age one year or above
- Suffering from β thalassemia
- Moderately to severely ill patients
- Not receiving any other medication for β thalassemia
- Not suffering from comorbidities like TB, Typhoid and Epilepsy

Processing of patients` data: In our study, patients of both genders were included in order to determine the role of hydroxyurea in reducing the need of blood transfusion and its safety profile. Patients who were registered in the thalassemia Centre for at least six months and patients with Hb level less than 6g/dL in two consecutive labs in initial 2 years of their lives were included in the study. They were categorized into different groups according to age, response to hydroxyurea, inheritance pattern, and gender as shown in table 1.

Table 1: Patients` groups based on various factors

Parameter	Categories
Age (in years)	1-10 years; 11-20 years; 21-30 years; 31-40 years.
Disease	β-Thalassemia Major; β-Thalassemia Intermedia; β-Thalassemia minor.
Gender	Male; Female.
Toxicity	Side effects; No side effects.
Patients response	Excellent response; Good response; Poor response.
Genetic tendency	Children with cousin marriage history; Children without cousin marriage history.
Chelating agents	Deferoxamine; Deferasirox; Deferiprone.
Therapeutic effects of different chelating agents	Controlled serum ferritin level; Uncontrolled serum ferritin level.

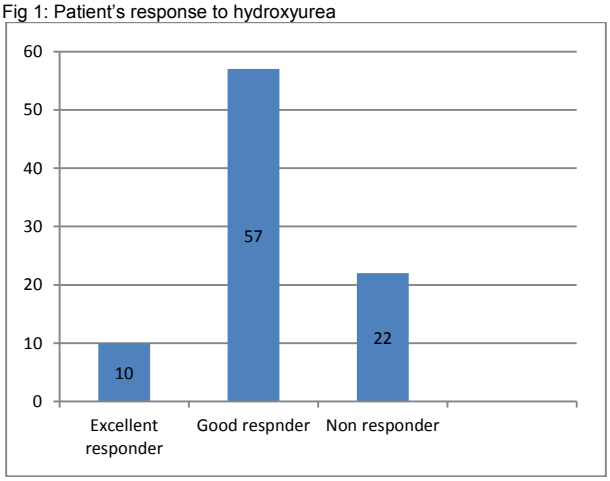
The dosage of Hydroxyurea was selected for the patients according to their weight. Red blood cell and platelet counts were monitored monthly. Various iron chelating agents were being used for treatment of iron overloading in patients. Data was collected from patient's clinical records. A performa was designed containing the information about patients which included their diagnosis, treatment history, family history, blood transfusion details(before and after using hydroxyurea), toxic effects of hydroxyurea, iron toxicity and detail of the chelating agents being used by the patients. All the data recorded was kept confidential and was used only for the study purpose. The data collected was then analyzed with the help of descriptive statistics. The results were calculated using "dependent/paired sample t test" and presented in form of graphs. Mean value for samples was calculated, standard deviation was also calculated and finally probability factor was observed.

RESULTS

The purpose of this study was to evaluate the reduction of blood transfusion need of thalassemia patients with hydroxyurea therapy. Out of eighty seven patients included, 72 % were diagnosed with thalassemia major, 26% were diagnosed with thalassemia intermedia and 1% with thalassemia minor.

Based on gender, 57% subjects were male and remaining 43% were female patients. History of cousin marriage was positive in 87% cases indicating the role of genetics in this particular group of disorders. Majority of the patients were 1-10 years old (60%) while remaining were from 10-20 years (32%), 20-30 years (4.6%) and 31-40 years (3.4%). This indicates that the disease appears in early age and then these children keep on getting medical help as the condition is not completely cured. One of the important management strategies in these patients is to transfuse blood to maintain their hemoglobin level. In addition, drugs called fetal hemoglobin gene inducing agents such as hydroxyurea are also used in these patients. We have analyzed the impact of this therapy to produce a reduction in transfusion requirements. Our findings reveal that 11% patients showed excellent response to hydroxyurea, 65.5% were good responder and 25% were non responder to hydroxyurea. It was observed that 99% patients did not experience any toxic effect of hydroxyurea. The best results of hydroxyurea were seen in thalassemia intermedia patients as all patients showed excellent response to HU therapy. They all went off their transfusion needs. Fig. 1 below depicts the distribution of response pattern in all patients.

Fig 1: Patient's response to hydroxyurea



DISCUSSION

Hydroxyurea is widely used for β-thalassemia patients, particularly in transfusion-dependent patients, as it reduces blood transfusion needs. With low number of transfusion, lower will be the iron overloading and usage of chelating agents which have their own side effects. Deferoxamine injections for iron chelation have been used for about 30 years in patients with transfused iron overloads. Although life expectancy has increased in transfusion dependent anemia patients due to use of deferoxamine, yet cardiac disorders due to myocardial iron storage account for most of the deaths in young adults suffering from thalassemia major, related clinical disorders and their complications. It has been a prime target for hematologists to minimize cardiac disease by improving iron chelation. The strategies used for this purpose include developing oral iron chelators as well as regular evaluation of iron status in body and cardiac tissue. These strategies have shown success over a period of many years. FDA has approved a new oral chelator, deferasirox, recently. Deferasirox at the dose of 20 to 30 mg/kg/day reduces hepatic iron in patients suffering from thalassemia. Deferiprone is reported to reduce/ unload cardiac iron at a rate faster than deferoxamine. This report is based on a randomized trial which relied on cardiac magnetic resonance image studies[16].

Our study results are consistent with previous clinical studies. For example, Jain and Dadhich conducted a similar study

in 2018 in India. Their study included 60 patients of β-thalassemia major. These patients used oral hydroxyurea (8-15mg/kg/day). The patients were followed up over a period of six months. Their study results also revealed reduction in rate of blood transfusion in thalassemia patients and iron load. They evaluated clinical response in their patients based on increased hemoglobin as well as reduction in levels of HbF, serum ferritin and blood transfusions[14].

A study by Ansari and colleagues, conducted on 152 patients, has reported that therapeutic effects of HU were observed two months after regular consumption of HU by the patients[17]. Another study has reported increase in level of Hb and reduction in serum ferritin with HU treatment[18]. A report by Italia and co-researchers has presented 74% good response in patients with thalassemia intermedia. Further, one third of the patients included had shown to require half the number of transfusions compared to their need before the therapy[19]. Bradai and co-workers have also reported up to 70% decrease in blood transfusion in half of the subjects included in their study. They have used HU at a dose of 17mg/kg in 45 thalassemia major patients. Furthermore, they have mentioned that a better response was observed particularly in those patients who needed first blood transfusion at an older age, who already had high level of baseline Hb and who have had spleenectomy. In addition, they did not find a positive impact on transfusion reduction by increasing dosage of HU[13].

Another study focusing on reduction of transfusions in 133 thalassemia patients with HU therapy has reported that over 60% of the patients included in study went off transfusion and 23% required only occasional (1-2 times per annum) transfusionss[20].

The results of our study also indicate significant reduction in blood transfusion need of thalassemia patients with HU therapy. Out of 87 patients, 66 patients required less transfusion after treatment with HU and 21 patients did not respond to HU at all. After Hu therapy, HbF level in “good” and “excellent” responders was high compared to non-responders (P <0.001). Total patients included in this study were 87. Among this 72% patients were diagnosed with thalassemia major, 26% were diagnosed with thalassemia intermedia and 1 % was of thalassemia minor. 11.5% patients showed excellent response to hydroxyurea, 65.5% were good responder and 25% were non responder to hydroxyurea. Thalassemia was more prevalent in male (57%) as compare to female (43%). Thalassemia was observed in children of cousin marriage (87%) more as compare to children of non-cousin marriage (12.6%). Thalassemia was found more prevalent in children of age ranging from 1-10 years (60%), its prevalence in children of age ranging from 10-20 years was 32%, 4.6% was the prevalence rate in children of age ranging from 20-30 years and 3.4% in children of age more than 30 years. 99% patients did not experience any toxic effect of hydroxyurea. The best results of hydroxyurea were seen in patients of thalassemia intermedia patients, every patient showed excellent response to HU therapy. 100% patients of thalassemia intermedia stopped requiring transfusion. Additionally, data of blood iron levels of patients was also analyzed for patients using chelating agents. Deferasirox showed good results among other two chelating agents in controlling serum ferritin as it is easy to administer.

Scientists, physicians and clinical researchers still need immense work to do to make the HbF induction therapy to become the part of standard treatment for patient having β thalassemia. To know the exact mechanism of action of currently known and newly identified agents, studies and efforts must go on along with different trials and clinical programs to establish the efficacy and safety of these HbF agents and also to further evaluate their effectiveness.

CONCLUSION

Hydroxyurea (HU) is the most widely studied HbF inducer and it can be safely prescribed to some of transfusion-dependent β-thalassemia patients in order to reduce the needs of blood transfusion. Blood transfusion costs and disease complications are also minimized by using HU. It is a safe drug, as it causes no major side effects other than cytopenia so it should be given to those patients who are regular in their follow up. It can safely and effectively counter extra medullary hematopoiesis and increase the Hb level in β-thalassemia intermedia and β-thalassemia major.

Conflict of interest: Nil

REFERENCES

1. Thein SL. Molecular basis of β thalassemia and potential therapeutic targets. Blood Cells Mol Dis. 2018; 70: 54-65.
2. Lal A, Wong TE, Andrews J, Balasa VV, Chung JH, Forester CM et al. Transfusion practices and complications in thalassemia. Transfusion. 2018;58(12):2826-2835.
3. Musallam KM, Taher AT, Rachmilewitz EA. β-thalassemia intermedia: a clinical perspective. CSH Perspect Med. 2012;2(7):a013482.
4. Musallam KM, Taher AT, Cappellini MD, Sankaran VG. Clinical experience with fetal hemoglobin induction therapy in patients with β-thalassemia. Blood. 2013;121(12):2199-2212.
5. Khan MI, Khan HN, Usman M. Beta thalassemia trait: Diagnostic importance of haematological indices in detecting beta thalassemia trait patients. Professional Med J. 2018;25(04):545-550.
6. Kantharaj A, Chandrashekar S. Coping with the burden of thalassemia: Aiming for a thalassemia free world. Glob J Transfus Med. 2018;3(1):1-5.
7. Tanveer T, Masud H, Butt ZA. Are people getting quality thalassemia care in twin cities of Pakistan? A comparison with international standards. Int J Qualit Health C. 2018;30(3):200-207.
8. Ayugi B. Knowledge, attitude and practices of health workers towards sickle cell screening in Tororo District, Uganda: Makerere University; 2018.
9. Singh A, Xu Y-J. The cell killing mechanisms of hydroxyurea. Genes. 2016;7(11):99.
10. Zohaib M, Ansari SH, Shamsi TS, Zubarev RA, Zarina S. Pharmacoproteomics profiling of plasma from β-thalassemia patients in response to Hydroxyurea treatment. J Clini Pharmacol. 2019;59(1):98-106.
11. Ataga KI, Cappellini MD, Rachmilewitz EA. β-Thalassaemia and sickle cell anaemia as paradigms of hypercoagulability. Brit J Haematol. 2007;139(1):3-13.
12. Chatterjee T, Chakravarty A, Chakravarty S. Hydroxyurea responses in clinically varied beta, HbE-beta thalassaemia and sickle cell anaemia patients of Eastern India. Ann Hematol. 2018;97(5):893-898.
13. Bradai M, Abad MT, Pissard S, Lamraoui F, Skopinski L, Montalembert MDe, et al. Hydroxyurea can eliminate transfusion requirements in children with severe β-thalassemia. Blood. 2003;102(4):1529-1530.
14. Jain JK, Dadhich SK. Efficacy of Hydroxyurea in Thalassemia major patients. Paripex Indian J Res. 2017;6(5): 45-46
15. Zhu J, Chin K, Aerbajinai W, Kumkhaek , Li H, Rodgers GP. Hydroxyurea-inducible SAR1 gene acts through the Giα/JNK/Jun pathway to regulate γ-globin expression. Blood. 2014;124(7):1146-1156.
16. Neufeld EJ. Update on iron chelators in thalassemia. Hematology Am Soc Hematol Educ Program. 2010;2010(1):451-455.
17. Ansari SH, Shamsi TS, Ashraf M, Perveen K, Farzana T, Bohray M et al. Efficacy of hydroxyurea in providing transfusion independence in β-thalassemia. J Pediat Hematol Onc. 2011;33(5):339-343.
18. Alebouyeh M, Moussavi F, Haddad-Deylami H, Vossough P. Hydroxyurea in the treatment of major β-thalassemia and importance of genetic screening. Ann Hematol. 2004;83(7):430-433.
19. Italia KY, Jijina FJ, Merchant R, Panjwani S, Nadkarni AH, Sawant PM. et al. Response to hydroxyurea in β thalassemia major and intermedia: experience in western India. Clin Chim Acta. 2009;407(1-2):10-15.
20. Yavarian M, Karimi M, Bakker E,Harteveld CL, Giordano PC. Response to hydroxyurea treatment in Iranian transfusion-dependent beta-thalassemia patients. Haematologica. 2004;89(10):1172-1178.