Pakistan Journal of Pharmaceutical Research
Faculty of Pharmacy, Bahauddin Zakariya University Multan, Pakistan
ISSN: 2410-6275 **July, 2018** **DOI:** 10.22200/pjpr.2018253-59

Research Article

Analysis of the cost of treating hydroxyurea versus chelating agent with blood transfusion in pediatric patients with thalassemia: a retrospective analysis

Muhammad Fawad Rasool, Gul-e-Nokhaze, Muhammad Nasir Kalam, Syed Nisar Hussain Shah, Abdul Majeed*
Faculty of Pharmacy Bahauddin Zakariya University Multan, Pakistan

Received: Jun, 17, 2019
Revised: Dec, 8, 2019
Accepted: Jun, 27, 2020
Online:

Abstract

Background: *Thalassemia is a group of genetically inherited blood disorders due to defective haemoglobin chains. Patients require continuous blood transfusions throughout the life which results in iron overload and toxic injury to various organs. So, there is always a need for chelation therapy which further increase the cost of therapy and affect the quality of life of patients.* ***Aim of the Study:*** *This study was conducted to analyze and compare the cost of treatment for Hydroxyurea and Chelating agents with blood transfusions in thalassemia, their clinical outcomes and success of therapy.* ***Methodology:*** *It was a retrospective cohort study conducted on pediatric thalassemia patients in tertiary care hospitals of Multan and Khanewal, Pakistan for six months.* ***Results:*** *The average cost of treatment in terms of direct medical cost in HU and BT treatments were Rs:1105.25 ± 392.62 and Rs:14219.27 ± 4124.22 respectively. Hydroxyurea treatment has relatively less (4.16%) adverse reaction than chelating agents (36.44%). Although it is not a blood group related disease, in this study, 54% of the sample have O +ive blood group.* ***Conclusion:*** *Hydroxyurea is better, both in terms of safety and cost of treatment than chelating agents to address iron overload with blood transfusion therapy in thalassemia.*

Keywords: Cost Analysis, Thalessemia, Blood Tansfusion, Hydroxy Urea

Introduction

Thalassemia is a genetic defect characterized by destruction of red blood cells. The name thalassemia is derived from a combination of two Greek words Thalassa meaning the sea (Mediterranean sea) and “anaemia” meaning weak blood (Manzon, 2007, Cohen AR, 2004). Professor. Cooley Thomas, a paediatrician in the USA, first described the clinical characteristics of this disorder in patients of Italian origin in 1925. The name thalassemia was coined by the noble prize winning pathologist George Hoyt Whipple (Manzon, 2007). It is a group of genetically inherited blood disorders in which the body synthesizes abnormal chains of haemoglobin (Hb), an oxygen-carrying protein of red blood cells, which leads to excessive destruction of red blood cells resulting in the development of hemolytic anaemia (Cohen AR, 2004). Thalassemia is a major health problem placing an immeasurable emotional, psychological and economic burden on millions of people around the world (Ho *et al.*, 2006).

Most prevalent types of thalassemia are α and β-thalassemia due to mutant translation of mRNA results in the synthesis of defective α and β chains respectively (CAMPBELL, 2009). Genetically, in a carrier state, there is only one α gene depletion while in minor α-thalassemia patients have lost two α globin genes. In this condition patients have small red cells and mild anaemia. In intermediate α-thalassemia, haemoglobin H disease, patients have severe anaemia and often require a blood transfusion to survive. Major α-thalassemia also called *Hydrops fetalis*, is a condition when there are no α-genes are present. Infants with α thalassemia are born normal but develop anaemia and splenomegaly by the end of their first year (CAMPBELL, 2009, Higgs and Weatherall, 1983). Beta-Thalassemia is further divided into three

***Corresponding Author:** Abdul Majeed
Address: Faculty of Pharmacy Bahauddin Zakariya University Multan, Pakistan
Email address: abdulmajeed@bzu.edu.pk

types Minor, Intermediate, Major. Minor β-thalassemia, also known as thalassemia trait, a condition in which one of the two β globin genes is abnormal but this defect is not great enough to cause problems in the normal functioning of the haemoglobin. In intermediate β-thalassemia, there are two abnormal genes and causes moderate to severe anemia. Major β-thalassemia, also known as Cooley's anemia, is the most severe form in which there is a complete lack of β globin production, preventing the production of significant amounts of HbA. The severe imbalance of globin chains results in ineffective erythropoiesis and severe microcytic hypochromic anemia (CAMPBELL, 2009, Galanello and Origa, 2010).

In past, the only treatment of Thalassemia was blood transfusion (BT). Several complications are associated with BT i.e. splenomegaly, iron overload in lungs, heart, liver, endocrine glands and hydroxyl free radicals. Hydroxyl free radicals accelerate tissue damage, which causes oxidative stress (Viprakasit V, 2009, JB, 2005, Morris CR, 2006, Olivieri NF, 1997). The hemostatic ability of the human body to prevent iron overload by strong binding of transfused iron with plasma proteins is limited. Iron overload is a major complication associated with all conditions where blood transfusion is needed. Accumulation of iron in vital organs of the body may result in comorbid diseases such as diabetes mellitus, chronic liver disease, cardiac dysfunction, hypothyroidism, hypoparathyroidism, and hypogonadism (Viprakasit V, 2009, JB, 2005, Morris CR, 2006, Olivieri NF, 1997, Cabantchik ZI, 2005, CA, 2010, Hashemi *et al.*, 2009). There is no known physiological process exists in humans to remove excess accumulated iron due to blood transfusions. Therefore, iron Chelating therapy is required to neutralize iron overload toxicity in blood transfusion-dependent patients. So for that reason, iron chelators such as intravenous deferoxamine, Oral deferipron and deferasirox were given along with blood transfusion in thalassemia. These agents bind with the extra iron present in the plasma and eliminate it from the body but this therapy costs very high and it eliminates complications of blood transfusion to some extent. Short elimination half-life and poor bioavailability are the major drawbacks of this supportive treatment (Cohen AR, 2004, EJ, 2006, JL, 2007). Certain drugs such as hydroxyl urea (HU) increases fetal haemoglobin among newborn and total haemoglobin levels among adult patients of thalassemia or sickle cell anemia (Farhad Zamani MD, 2009).

Cost of hydroxyl urea is a major obstacle to use it as a first option to manage blood transfusion-related complications in thalassemia. Previously many studies had calculated direct and indirect medical cost associated with the treatment of thalassemia with BT and HU(Ho *et al.*, 2013, Zhang *et al.*, 2011, Lee *et al.*, 2014, Scalone *et al.*, 2008, Taher and Cappellini, 2009, Zamani *et al.*, 2009, Delea *et al.*, 2007, Hashemi *et al.*, 2009, Algiraigri, 2015, Kim and Kim, 2009) but no such type of studies was conducted in Pakistan.

Aim of the Study

This study was conducted to analyze and compare the cost of treatment for Hydroxyurea and Chelating agents with blood transfusions in thalassemia, their clinical outcomes and success of therapy.

Methodology

It is a retrospective cohort study in which fifty (50) pediatric patients of both genders were included during the period of six months from April to September 2017 after approval from the ethical committee of Department of Pharmacy BZU Multan, Pakistan and Medical superintendents (MS) of hospitals from where data was collected. Drug charts were used to estimate the cost, adverse drug reaction (ADR's), clinical outcomes and success of therapy of in thalassemia patients treated with HU and Chelating agents in blood transfusion therapy.

Study Setting

This study was conducted in the Institute of Children Complex Hospital (ICCH), Nishter Medical University and Hospital (MMU&H) Multan and District Head Quarter Hospital (DHQ) Hospital Khanewal, Pakistan.

Inclusion criteria

Patients that were suffering from the intermediate and major thalassemia were included in this study.

Exclusion criteria

Patients with minor thalassemia or those that are not properly diagnosed and sickle cell anaemia were not included in this study.

Table 1: Disease stage and demographic Characteristics

Thalassemia Type (n=50)	
Thalassemia major	n=41
Thalassemia intermediate	n=09
Gender	
Male	n=32
Female	n=18
Age	0.5- 16 years
Height	45 cm – 147cm
Weight	4.8-45 kg

Results

In this study total, 50 patients of thalassemia were enrolled, their demographic and disease stage distributions are given in Table 1. Out of these 50 enrolled patients, 26 were receiving BT treatment while 24 were treated with HU regimen.

Four major complications were reported with BT treatment and their prevalence is represented in Table 2. Adverse effects observed with HU therapy are neutropenia and thrombocytopenia in about 4.16% of patients which are reversible and are resolved by short discontinuation of therapy or reducing the dose to16mg/kg.

Table 2: Adverse reactions reported with Chelating therapy

Iron overload	**19.2% (5)**
Splenomegaly	7.7% (2)
Liver enlargement	7.7% (2)
Skin Rash	3.84% (1)

As thalassemia is not blood group related disorder but in this study patients with positive blood groups and specifically O+ individuals were mostly affected with thalassemia and surprisingly their parents were also belonging to positive blood groups. About 54% of the patients had O+ blood group and other 46% of patients had other positive blood groups as shown in figure 2. Although data is insufficient to establish a statistical correlation between blood group type and thalassemia, further investigations will provoke from this fact that these O+ patients and their parents may have genes for thalassemia.

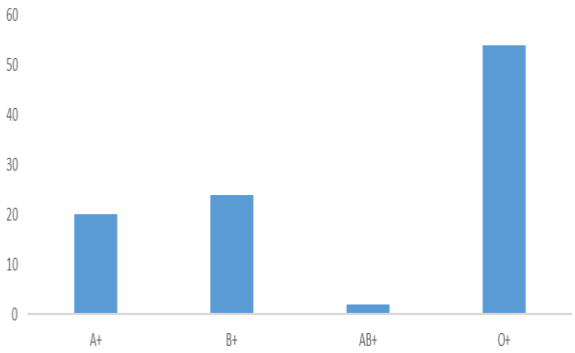

Figure 1: Relationship of Thalassemia with blood group type.

Per unit prices of medicines, surgical and supplies used for BT, HU and iron chelation therapy are mentioned in Table 3. The average cost of treatment in terms of direct medical cost in HU and BT treatments were Rs: 1105.25 ± 392.62 and Rs: 14219.27 ± 4124.22 respectively. This cost was calculated simply by adding per unit price of all the medicines, surgical and supplies used per day and multiply per day cost with a total number of hospital stay which yields into the total direct medical cost of treatment. Direct medical cost with HU treatment can be reduced in thalassemia patients who are receiving blood transfusion therapy. Therefore, hydroxyl urea treatment is superior to blood transfusion treatment both in terms of cost and fewer adverse effect.

Table 3: Per unit price of medicines/Surgical and supplies used in BT and HU treatments.

	Pack size	Per Unit Cost in PKR
Medicines/Surgical and supplies Used in Chelating agent Therapy		
Inj. Deferoxamine 500 mg (Desferal)	1×10s	Rs:216.9/-
Tab. Deferoxamine (Osveral) 125mg/250mg/500mg	1×1s 1×28s	Rs:94.64/-, Rs:156.0/-, Rs:260.0/-
Blood Transfusion Cost	Once	Rs:1000-1200/-
Medicines/Surgical and supplies Used in HU Therapy		
Cap. Hydroxyurea 500 mg	100s	Rs:13.3-11.68/-
Tab. Tocopherol (Vitamin-E) 200mg/400mg/600mg	10×10s	Rs:2.6/-, Rs:4.4/-, Rs:6.0/-
Tab. Folic Acid 5mg	100s	0.4672/-
Syp. Iron Hydroxide Polymaltose complex 50mg/5ml	60 ml	Rs:70/-

Discussion:

In early life, Blood transfusion was the only treatment available for the thalassemia patients and the transfusion causes certain adverse effects such as skin rash, splenomegaly, liver enlargement and iron overload. Hydroxyurea chelation therapy was the only available treatment for patients with iron overload due to repeated blood transfusions in thalassemia. The most common iron chelates used at that time for the thalassemia treatment with blood transfusion were deferoxamine and deferasirox. Iron chelates cause various diseases which include cardiac diseases, diabetes mellitus, hypogonadism, and hypothyroidism and also it was very costly for the patients to manage and arrange blood for their children (Wan-Ling Ho, 2011). Results of this study generate a piece of evidence that the newly available anti-cancer drug HU is much better both in terms of safety due to lesser adverse effects and economical than blood transfusion therapy. Gamma globin genes reactivation play a significant role in the treatment of thalassemia and HU is responsible for up-regulation of gamma chain synthesis and increased fetal haemoglobin (HbF) hemoglobin production. This drug has the potential to be used for the treatment of thalassemia because of its effects on the overproduction of fetal haemoglobin (HbF) and lesser clinical adverse complications. Currently, in Pakistan use of hydroxyl urea as a chelating agent is very low.

Cost of treatment is the total expense of the treatment or therapy. Pharmacoeconomics is the comparison of two or more alternative courses of action (Interventions) in terms of both their costs and consequences. There are several types of Pharmacoeconomics studies distinguished by the experts in economics with the difference of the consequences measured. The types of Pharmacoeconomics studies include cost-maximization analysis,

cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis (Drummond MF, 2005). Cost of treatment studies is a type of Pharmacoeconomics in which we measured all direct, indirect medical and non-medical cost associated with one specific treatment or intervention. Results of one analysis can be compared with the results of others to compare which treatment costs less. The present study elaborates results of the cost of treatment of fifty patients of thalassemia major and intermediate which are either receiving a blood transfusion or HU therapy. The effect of these two treatments on total Hb, transfusion requirements, and the level of ferritin requirement was the most significant observations of this study. This study explained better clinical and economic outcomes with HU over blood transfusion in thalassemia. HU showed improvements in clinical outcomes in a very short time and there was no significant relationship of gender with HU treatment. There is an increased Hb production with increased utilization of iron and degradation of ineffective erythropoiesis with HU treatment makes it most acceptable chelating agent. HU treatment was much effective and it didn't have any hematologic toxicity except neutropenia and thrombocytopenia in about 1% patients but was resolved after short discontinuation of therapy (Bradai *et al.*, 2003). Long term use of hydroxyl urea can be associated with the development of carcinogenic effects but in a five year follow up study, there were no malignancies even leukaemia observed (Farhad Zamani MD, 2009). This study shows that HU can be an effective and safe treatment for major and intermediate thalassemia patients in long term therapy but the effects of HU in thalassemia patients are still under study. Some of the major adverse effects observed with blood transfusion are splenomegaly, liver enlargement, skin rash and most common of which is iron overload which further causes cardiac dysfunction, diabetes, liver disease, hypogonadism, hypothyroidism and hypoparathyroidism. These adverse effects can be overcome by treating the patient with HU. QoL is not measured directly as it requires certain parameters such as quality-adjusted life years (QALY) and disease affected life years (DALY). But here we are not measuring it directly and the effect of both therapies on patient QOL and patient satisfaction is measured indirectly. As HU causes a reduction in spleen and liver enlargement and also increases the transfusion interval in major patients and eliminate in intermedia patients and some major patients (Bradai *et al.*, 2003). Patients are more adhere to HU therapy because it is an oral drug and no side effects are seen up till now because difficulty arises for a patient to arrange blood and to manage major side effects. Patients also find it difficult to tolerate repeated blood transfusions in a month so QoL is more improved with HU therapy than transfusion therapy.

Limitations

Firstly, a very small sample size can't exactly showcase the comparison of treatment success with a cost. Although results were satisfactory in support of the hypothesis, for more strong evidence of low-cost treatment and better clinical outcome, a large data set is required. Secondly, Patients who have Xmn1 polymorphism they only respond to HU therapy and response is 100% Xmn1 polymorphism is a known factor, which increases fetal haemoglobin

production. Among the inherited disorders of the blood, Thalassemia and Sickle cell disease (SCD) constitutes a major bulk of genetic diseases (Sanjy pandey, 2016). Although in some patients there are some gene mutations due to which HU is non-responsive and the only treatment for those patients is blood transfusion. This is the only drawback of HU treatment and this is still under study.

Conflict of interest

All authors don't have any conflict of interest.

References:

Algiraigri, A. 2015. A Meta-Analysis of Hydroxyurea Use for β-thalassemia: Implications for Clinical Practice and Medical Education. University of Calgary.

Bradai, M Abad, MT Pissard, S Lamraoui, F Skopinski, L and De Montalembert, M. (2003). Hydroxyurea can eliminate transfusion requirements in children with severe β-thalassemia. Blood, **102**: 1529-1530.

Ca, F. (2010). Iron chelation therapy in myelodysplastic syndromes. Am J Health Syst pharma: S10-4.

Cabantchik Zi, BW. (2005). Plasma iron in iron overload. Best pract Res Clin Haematol, 277-87.

Campbell, JS. (2009). Alpha and beta thalassemia. American family physician, **80**.

Cohen Ar, GR, Cunningham Mj. (2004). Thalassemia. Hematology Am Soc Hematol Educ Programe, 14-34.

Delea, TE Edelsberg, J Sofrygin, O Thomas, SK Baladi, JF Phatak, PD and Coates, TD. (2007). Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. Transfusion, **47**: 1919-1929.

Drummond Mf, SM, Torrance Gw. (2005). Method for the economic evaluation of health care programmes. Oxford University Press, 1245-53.

Ej, N. (2006). Oral chelators deferox and deferiprone for transfusional iron overload in thalassemia major. Blood, 3436-41.

Farhad Zamani Md, RSM. (2009). Hydroxyurea therapy in 49 patients with major beta thalassemia. Arch Iranian Medicine, 295-97.

Galanello, R and Origa, R. (2010). Beta-thalassemia. Orphanet journal of rare diseases, **5**: 11.

Hashemi, A Abrishamkar, M Jenabzade, AR and Eslami, Z. (2009). Hydroxyurea can reduce or eliminate transfusion requirements in children with major and intermediate thalassemia. Iranian Journal of Blood and Cancer, **1**: 147-150.

Higgs, D and Weatherall, D. (1983). Alpha-thalassemia. Current topics in hematology, **4**: 37.

Ho, W-L Chung, K-P Yang, S-S Lu, M-Y Jou, S-T Chang, H-H Yang, Y-L Lin, D-T and Lin, K-H. (2013). A pharmaco-economic evaluation of deferasirox for treating patients with iron overload caused by transfusion-dependent thalassemia in Taiwan. Journal of the Formosan Medical Association, **112**: 221-229.

Ho, W Lin, K Wang, J Hwang, J-S Chung, C Lin, D-T Jou, S-T Lu, M and Chern, J. (2006). Financial burden of national health insurance for treating patients with transfusion-dependent thalassemia in Taiwan. Bone marrow transplantation, **37**: 569.

Jb, P. (2005). Monitoring and treatment of iron overload. Semin Henatol, 14-8.

Jl, S. (2007). Deferasirox. Am J Health Syst Pharm, 606-16.

Kim, J and Kim, Y. (2009). A Time-Cost Augmented Economic Evaluation of Oral Deferasirox versus Infusional Dereroxmine for Patients with Iron Overload in South Korea. Value in health, **12**.

Lee, TA Von Riedemann, S and Tricta, F. (2014). Cost-utility of chelators in transfusion-dependent β-thalassemia major patients: a review of the pharmacoeconomic literature. Expert review of pharmacoeconomics & outcomes research, **14**: 651-660.

Manzon, VS. (2007). B-thalassemia: the anemia coming from the sea. Intensive course in biological anthropology 1st summer school of the European Anthropological association, 16-30.

Morris Cr, SS, Walters Mc. (2006). Clinical Hemoglobinopathies. Curr Opin Hematol, 407-18.

Olivieri Nf, BG. (1997). Iron chelation therapy and the treatment of thalassemia. Blood, 739-61.

Sanjy Pandey, SP, Rahasya Mani Mishra, Renu Saxena. (2016). Modulating effect of the Xmn1 polymorphism in Indian sickle cell patients. Mediterranean Journal of Hematology and Infectious Diseases.

Scalone, L Mantovani, LG Krol, M Rofail, D Ravera, S Grazia Bisconte, M Borgna-Pignatti, C Borsellino, Z Cianciulli, P and Gallisai, D. (2008). Costs, quality of life, treatment satisfaction and compliance in patients with β-thalassemia major undergoing iron chelation therapy: the ITHACA study. Current medical research and opinion, **24**: 1905-1917.

Taher, A and Cappellini, MD. (2009). Update on the use of deferasirox in the management of iron overload. Therapeutics and clinical risk management, **5**: 857.

Viprakasit V, L-L. (2009). Iron chelation therapy in the management of thalassemia. Int J Hematol, 435-45.

Wan-Ling Ho, K-PC, Szu-Sheng Yang. (2011). A pharmaco-economic evaluation of deferasirox for treating patients with iron overload caused by transfusion-dependent thalassemia in Taiwan. Formosan medical association, 221-229.

Zamani, F Shakeri, R Eslami, S-M Razavi, S-M and Basi, A. (2009). Hydroxyurea therapy in 49 patients with major beta-thalassemia. Arch Iran Med, **12**: 295-297.

Zhang, B Donga, PZ Corral, M Sasane, M Miller, JD and Pashos, CL. (2011). Pharmacoeconomic Considerations in Treating Iron Overload in Patients with β-Thalassaemia, Sickle Cell Disease and Myelodysplastic Syndromes in the US. Pharmacoeconomics, **29**: 461-474.