Research Article

Study on Effectiveness of Transfusion Program in Thalassemia Major Patients Receiving Multiple Blood Transfusion

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ABSTRACT

Introduction: Beta thalassemia is the most common monogenic hereditary haemoglobin disorder, which poses a major health burden. Patients require repeated blood transfusions. The transfusion of blood has many side effects like iron overload, transfusion-related infections etc. The objectives of the study were to assess the adequacy of blood transfusion for thalassemia patients and to determine the magnitude of transfusion-transmitted infections among those patients.

Methods: A cross-sectional study was conducted at Rabindranath Nath Tagore Medical College, Udaipur for 1 year. The blood samples from the patients were taken from the patients attending for blood transfusion in the transfusion centre MB Blood bank and Hospital for 1 year dated from 01.10.2017 to 30.9.2018 to check for the pre-transfusion haemoglobin, serum ferritin level and hepatitis B, C and HIV infection.

Results: Among the 159 patients, 57(35.9%) patients had a mean haemoglobin level between 8-9 gm/dl, 69(43.6%) patients had a mean haemoglobin level of more than 9gm/dl and 32(20.5%) patients had a mean haemoglobin level was less than 8 gm/dl.10/159 (6.4%) patients had S. ferritin <1000 ng/ml. 149 (93.7%) patients were taking some form of chelation therapy. HIV was present in 1(0.62%) of cases i.e. only one case of HIV positive, 2(1.26%) cases had HBsAg positive, and 7(4.4%) cases had HCV positive.

Conclusions: Frequent Hb estimation will help to maintain the adequacy of blood transfusion, effective chelation measures to keep serum ferritin levels below 1000 ng/ml to avoid the systemic effects of iron overload and proper screening of the blood before transfusion can help in reducing these transfusion-transmitted infections

Keywords: Thalassemia, Ferritin level, chelation therapy, Transfusion-related infections.

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INTRODUCTION

Among all childhood diseases, haematological and hereditary diseases are the most life-threatening disease conditions which affect in their early life. It affects upon birth, severely affecting their ability to survive on their own due to chronic anaemia resulting from an inherited haemoglobin disorder. With currently available medical treatment, afflicted children have a substandard quality of life and a shortened life expectancy. The selective pressure that has made thalassemias so common is not known but is assumed to relate to the geographic distribution of Malaria.[1,2]Hemoglobinopathies are more prevalent in certain malaria-prone parts of the world like India. Every year at least 5000 are diagnosed with thalassemia. South Asia contributes to at least 23% of the world's hemoglobinopathies. Thalassemia is one of the commonest single-gene disorders in India. The beta-thalassemia carrier ranges between 2.78 to 4% in India.[3] Among the world's total population, 4.5% are carriers of hemoglobinopathies, about 15 million people are thalassemia patients and 240 million people are carriers of B-Thalassemia. The largest concentration of thalassemia patients is seen in South Asia, Sri Lanka, Bangladesh, Pakistan, Middle East countries and Italy.[4]

All forms of Thalassemia like Thalassemia Minor, Thalassemia Major, Alpha-thalassemia, beta-thalassemia, and delta-thalassemia are transmitted only through heredity. The disease is passed on through parents who carry the Thalassemia gene in their cells. A 'carrier' has one normal gene and one Thalassemia gene in all body cells, a state sometimes called having the 'Thalassemia trait. Most carriers lead completely normal healthy lives.[5]In India, it is estimated that there are about 65,000-67,000 beta-thalassemia patients with around 9,000-10,000 cases being added every year. The carrier rate for the beta-thalassemia gene varies from 1 to 3% in Southern India to 3 to 15% in Northern India.[6] Its prevalence is high in ethnic groups among Gujarathies, Punjabis, Sindhis, Lohanas etc. Over 30 million people are carriers of the thalassemia gene in our country.[2,7]Thalassemia can cause life-threatening

situations and chronic ill health. They pose an economic and psychological burden on the affected individual and his family and society as a whole. Hence a detailed study needs to be conducted and steps should be taken to improve the quality of life of thalassemia patients and to prevent thalassemia through population screening and genetic counselling.[6]

Beta thalassemia is the most common monogenic hereditary haemoglobin disorder. Patients with beta-thalassemia major suffer from chronic anaemia due to hemolysis and ineffective erythropoiesis. Guidelines for the management of transfusion-dependent thalassemia as proposed by the Thalassemia International Federation involves regular red blood cell transfusion throughout life, usually administered every 3-5 weeks depending upon the transfusion needs of each individual to maintain pre-haemoglobin between 9-10.5 gm/dl.

Frequent transfusions result in the inevitable accumulation of iron. Patients may accumulate 5gm of iron per year following a transfusion of 25 units of blood per year. Increased gastrointestinal iron absorption due to increased hepcidin in thalassemia patients causes further accumulation of iron. Progressive deposition of iron leads to dysfunction and failure of major organs including the heart, liver, and endocrine glands such as the pituitary, thyroid, parathyroid, adrenal and endocrine pancreas. Therefore proper iron chelation therapy is mandatory for transfused patients with beta-thalassemia major. Regular assessment of iron status is essential for the efficient management of iron overload in beta-thalassemia major patients. Serum ferritin level correlates with the iron burden in the body. Serial measurements of serum ferritin levels are widely used worldwide as an easy and reliable method of assessing iron status in patients.[8] A regular blood transfusion regimen is confronted with numerous complications. In almost every patient, the transfusion requirement slowly increases over years. Various factors contribute towards this increased requirement including the development of hypersplenism, all immunisation against various blood group antigens, chronic infections, folate deficiency, aplastic crisis etc.[9]

Alloimmunisation to red cell antigens and transfusion transmissible infections are the major complications of transfusion, particularly for those who are chronically transfused. Some alloantibodies are hemolytic and may cause hemolytic transfusion reactions and may limit the possibility of further safe and effective transfusion, while others are clinically insignificant. Alloantibodies must be identified in the patient's serum before each transfusion so that compatible blood can be provided. The causes of alloimmunisation are not fully understood, however, studies suggest that the recipient's immune status, the difference in red cell phenotype between the donor and the recipient, and the number of units the patients receive are the main contributing factors.[10]

It is a common scenario in India; thalassemia major patients receive suboptimal transfusion and chelation therapy due to several reasons, financial and social causes, lack of specialized centres, and lack of safe blood transfusion services across the country. There are no adequate studies published on the adequacy of transfusion, morbidity and survival in thalassemia patients. Thus, the main objective of the study is to offer subjects affected by thalassemia the most efficacious treatment. There is a lack of studies in this region of the country describing the blood transfusion profile of Beta thalassemia major patients. Hence the present study was undertaken to assess the clinical data and blood transfusion profile of these patients.

The aim was to study transfusion requirements in thalassemia patients and the adequacy of transfusion in terms of pre-transfusion Haemoglobin level. Adequacy and regularity of chelation therapy were seen in terms of serum ferritin level and the prevalence of TTI among thalassemic patients was studied.

MATERIALS AND METHODS

Study design

This study was conducted among registered beta thalassemia major patients receiving regular blood transfusions at MB government hospital located in Udaipur city, Rajasthan state, India from 1st October 2017 to 30th September 2018.

All confirmed beta thalassemia major patients aged more than or equal to 3 years registered at MB Blood bank Udaipur, and receiving blood transfusions regularly at the same institute are included in this study.

Subjects

This cross-sectional study included 159 beta-thalassemia major patients whose ages ranged between 3yrs to 23yrs (mean 8.63+4.08 years). All patients were subjected to thorough history taking with special emphasis on blood transfusions regarding the age at which thalassemia was diagnosed, 1st time when blood was transfused, the total number of blood transfusions till now, rate of blood transfusion, type of received blood, and history of previous transfusion reactions in addition to the type of chelation and compliance to iron chelation therapy. Data regarding the chelation therapy were obtained from the diary maintained by the pediatric department for each thalassemic child. Serum ferritin and pre-transfusion haemoglobin assessment were done for all patients.

After explaining the procedure to the patients and acquiring informed consent from the patients or guardians, 4 ml of venous blood was drawn under complete aseptic conditions and divided into 1 ml on EDTA to perform ABO and Rhesus (Rh) blood grouping and haemoglobin level before transfusion. The other 3 ml was left to clot and centrifuged to separate the serum to perform the cross-matching and estimation of serum ferritin. Assessment of Pretransfusion haemoglobin was determined using a SAHLI'S HEMOGLOBIN ESTIMATION METHOD also known as the ACID HEMATIN METHOD.

Analysis of serum ferritin level was determined using ELECTROCHEMILUMINESCENCE IMMUNOASSAY. ECLIA is intended for use on Elecsys and cobas e immunoassay analysers. For testing transfusion-transmitted infections, samples are sent to RNT Medical college for HIV 1 and HIV 2 testing. A Rapid Tridot Test to detect antibodies to HIV 1 and HIV 2 in human serum or plasma is used. Samples are sent to the central lab of the pathology department for HBsAg and HCV testing. A Raid, a one-step test for the quantitative detection of Hepatitis B Surface Antigen in serum or plasma is done. A rapid test kit for HCV antibodies is done.

Clinical parameters

The records of all 159 patients were examined to obtain the following information from 1st October 2017 to 30th September 2018: Pre haemoglobin transfusion level, quarterly serum ferritin level, hepatitis B and C and HIV Serology.

Statistical methodology

Data were statistically described in terms of range, Mean+SD (Standard deviation), frequencies and percentages when appropriate. Comparison of quantitative variables between the study groups was done using the student t-test for independent samples in comparing two groups and the one-way analysis of variance (ANOVA) test in comparing more than two groups.

For comparing categorical data, a Chi-square test was performed. The exact test was used instead when the expected frequency was less than 5. A probability value (P value) less than 0.05 was considered statistically significant.

All statistical calculations were done using Microsoft Excel 2003(Microsoft corporation NY USA) and SPSS(Statistical Package for the Social Science, SPSS Inc, Chicago IL, USA) version 15 for Microsoft windows.SVG

Ethical consideration

The study protocol was approved by the ethical committee of our centre. Informed oral consent was obtained from each child's parents before participation in the study.

RESULTS AND DISCUSSION

Demographic details

Confirmed beta thalassemia major patients aged more than or equal to 3 years registered at our blood bank, and receiving blood transfusions regularly are 159.0ut of which 121(76.1%) cases were males and (38)23.9% cases were females. The male: female ratio is 3.5:1. Most common age group in our study was 8-12 years with 70 (44.1 %) cases, followed by 63 (39.6%) cases in the age group 3-7 years, 21 (13.2%) cases were in the age group 13-17 years and 5 (3.1%)cases were in age group >17 years. The Mean±SD of age is 8.63±4.08. Majority of patients were of blood group B+ 59(37.1%) followed by O+ 57(35.8%) A+ 35(22.0%), AB+ were 6(3.77%) and B- was 2(1.25%). Here, 87(53.5%)patients were diagnosed at 7-11 months of their age followed by 57(35.8%) cases diagnosed at 3-6 months of age and 17(10.7%) patients were diagnosed after or during 1 year of their age.

In our study there is male preponderance with a male: female ratio is 3.5:1. In consistent with this study Pattanashetti et al found male preponderance in their study.[11]In their study majority (80%) of the patients were males and the male-to-female ratio was 4:1. Similarly, a study done by Khalifa et al[12]showed a majority of patients were males. The sex distribution pattern observed in the present study was similar to other studies from Kolkata[13] and Rawalpindi.[14]In our study, the most common age group was 8-12 years with 44.1 % cases, followed by 39.6% cases in the age group 3-7 years. Consistent with this study Pattanashetti et al found the most common age group was 10-12 years with 51.4% cases followed by 25.7% cases in the 13-15 years age group.[11] Sarkar et al found majority of patients were in the age group 5-9 years (35.3%)[3]The mean age of patients in our study is 8.6±4.08. Karunaratna et al found mean age of 10.97±5.9.[8]

In our study, B+ and O+ were the most common blood groups of patients followed by A+. In concordance with this study Sarkar et al also found similar results. In their study, B+ was present in 37% and O+ was present in 36.2% of cases.[3] Sinha et al also found O+ and B+ were the most common blood group among ß-thalassemia patients.[15]Mohsin MY et al studied the frequency distribution of haemoglobin variant and ABO blood groups among thalassemia patients from Ibn-Al-Baladi hospital in Baghdad/Iraq stated the same fact of O blood group being the common incidence (59.1%) and AB with the least common occurrence of the disease ß-thalassemia.[16]In our study, most of the patients (53.5%) were aged between 7-11 months at the diagnosis of β thalassemia major and 35.8% of patients were aged between 3-6 months at the time of diagnosis. A study by Pattanashetti et al also found that most of the patients were aged between 7 to 12 months (45.71%) and 12 to 18 months (42.86%) at the diagnosis of β thalassemia major.[11]Samarakoon and Wijesuriya also found that the majority of patients (30 patients) were aged between 3-6 months followed by 21 patients aged between 7-11 months, 3 patients were aged between <3 months and 7 patients were aged between 1-5 years at the time of diagnosis of β thalassemia major.[17]

Pre-hemoglobin level and transfusion

57(35.9%) patients had a mean haemoglobin level between 8-9 gm/dl, 69(43.6%) patients had a mean haemoglobin level of more than 9gm/dl and 32(20.5%) patients had a mean haemoglobin level was less than 8 gm/dl. Mean haemoglobin distribution according to gender is shown in Table 1. Patients under the 3-7 years age group received nearly 55 times blood transfusion so far, patients under the 8-12 years age group received nearly 121 times blood transfusion, patients under the 13-17 years age group received nearly 171 times blood

transfusion and 5 patients which were more than 17 years received greater than 250 times blood transfusion so far.

Table 1: Mean haemoglobin distribution according to gender.

Gender	Mean Hb value	P value
Male	9.76+0.91	0.0001
Female	8.95+0.93	

In our study, only 20.5% of patients had a mean haemoglobin level below 8 gm/dl. In 35.9% of patients mean haemoglobin level reached between 8-9 gm/dl and in 43.6% of patients mean haemoglobin level reached more than 9 gm/dl. But a study by Sarkar et al found that even after transfusion 94% of the study participants have their haemoglobin levels below 7 gm/dl. Only 2 individuals got haemoglobin levels of more than 9 gm/dl.[3]Also in a study by Karunaratna et al, The mean pre-transfusion haemoglobin concentration was 8.15±1.21g/dl with a range of 4.00–10.3 g/dl and 37 patients (92.5%) were below the expected minimum haemoglobin concentration (9.5 g/dl).[8]

In our study as the age of patients increases the no. of transfusions increases. patients under the 3-7 years age group received nearly 55 times blood transfusion so far, patients under the 8-12 years age group received nearly 121 times blood transfusion, patients under the 13-17 years age group received nearly 171 times blood transfusion and 5 patients which were more than 17 years received greater than 250 times blood transfusion so far. The linear relationship between age and no transfusion was also studied by Koreti et al.[18]They found a linear relationship between the age of thalassemia major patients and the total number of blood transfusions received so far. With the increase in age, the cumulative number of blood transfusions received will increase.

Serum ferritin

Here, 10(6.4%) cases had serum ferritin level less than 1000 µg/l, 62(38.9%) had serum ferritin level between 1000-2000 µg/l, 52(32.7%) had serum ferritin level between 2001-3000 µg/l, 31(19.5%) had serum ferritin level between 3001-4000 µg/l , 4(2.5%) had serum ferritin level l greater than 4000 µg/l. Here, the mean serum ferritin level in the age group 3-7 years is 63(1549.5±338.1); in the age group 8-12 years is 71(2528.8±374.1); in the age group 13-17 years is 23(3609.7±318) and in age group >17 years mean ferritin level is 5(3971.6±369.2). The distribution of mean ferritin according to gender is shown in Table 2. Here, 10/159 (6.4%) patients had S. ferritin <1000 ng/ml. Hence these patients could be considered to be taking adequate chelation therapy. 149 (93.7%) patients were taking some form of chelation therapy. Out of these, 62(38.9%) patients were taking Deferiprone daily, 83(52.2%) taking Deferiprone daily and 4(2.5%) taking Desferrioxamine daily for 5 days a week.

Table 2: Distribution of mean ferritin according to gender

Gender	Mean Hb value	P value
Male	2252.4±812.5	0.0356
Female	2572±804.6	

In the present study majority of patients had serum ferritin levels between 38.9% had serum ferritin levels between 1000-2000 µg/l, 32.7% had serum ferritin levels between 2001-3000 µg/l, 19.5% had serum ferritin levels between 3001-4000 µg/l. Koreti et al found The serum ferritin concentration was less than 2000 µg/l in 30patients(50%), between 2001–4000 µg/ in 20 patients (33.3%) and rest 10 patients(17.7%) had serum ferritin levels >4000 µg/l. Majority of the patients with high serum ferritin concentration(>4000µg/l) (120). But in our study, we had 6.4% of cases whose serum ferritin level was maintained at less than 1000 µg/l and adequately chelated. Consistent with this Shah et al (105) found that 96 (67%) of the patients were taking some form of chelation therapy but out of them only 2 (2%) were adequately chelated (S. ferritin <1000 ng/ml).

In the present study, we found that mean serum ferritin level increases with age it was highest in patients greater than 17 years (3971.6±369.2), following this study by Koreti et al found similar results (120). The serum ferritin concentration was less than 2000µg/l in 30 patients (50%), between 2001–4000 µg/ in 20 patients (33.3%) and rest 10 patients (17.7%) had serum ferritin levels >4000 µg/l. The majority of the patients with high serum ferritin concentration(>4000µg/l) were aged more than 10 years

In our study, there is a significant difference (p-value=0.0001) in the mean Hb level in both sexes in males mean Hb level was 9.76±0.91 and in females mean Hb level was 8.95±0.93.

In our study mean serum ferritin level was high in females as compared to males with a statistically significant difference (P-value=0.0373). In concordance with this study, Koreti et al found that the Mean serum ferritin concentration of the female patients was 2986µg/l while in male patients it was 3245µg/l. There was no significant difference in mean serum ferritin concentration between the two groups (p = 0.54).[18]

In the present study, we found that only 10/159 (6.4%) patients had S. ferritin <1000 ng/ml. Hence these patients could be considered to be taking adequate chelation therapy. 149 (93.7%) patients were taking some form of chelation therapy. Out of these, 38.9% of patients were taking Deferiprone daily, 52.2% taking Deferiprone daily and 2.5% taking Desferrioxamine daily for 5 days a week. A study by shah et al found that only 9/142 (6.3%) patients had S. ferritin <1000 ng/ml and 7 out of these 9 patients were not taking any chelation. Hence only 2 (1.4%) patients could be considered to be taking adequate chelation therapy. 96 (67%) patients were taking some form of chelation therapy. Out of these, 89 patients were taking Kelfer (Deferiprone), 5 were taking Asunra

(Desferasirox), and 2 were taking Desferral (Desferrioxamine).[19]

Transfusion-transmitted infections

HIV was present in 1(0.62%) of cases i.e. only one case of HIV positive, 2(1.26%) cases had HBsAg positive,7(4.4%) cases had HCV positive and 149(97.3%) cases there was no transmission of infection through blood transfusion.

In the present study majority of cases (97.3%) had no transmission through blood transfusion and 6.28 had transfusion-transmitted infection out of them 0.62% cases i.e. only one case of HIV positive, 1.26% cases had HBsAg positive, 4.4% cases had HCV positive. Consistent with this study by Patel et al found that, among the 177 patients, 8.47% were affected by this. Among them, HIV contributed 3.95% while 2.26% each HBV and HCV. The prevalence of TTIs such as HCV, HIV, and HBsAg was 45%, 2%, and 2%, respectively in a study conducted by Neeraj et al,[20]which shows a quite high prevalence of HCV when compared with our study. While in a study by Ocak et al.[21] showed the prevalence of HBsAg, HCV, and HIV to be 0.75%, 4.5%, and 0%, respectively, which is also comparable to our study.

Adequacy is assessed by haemoglobin levels and serum ferritin levels after the transfusion. According to the study by Brittenham et al on the efficacy of deferoxamine in 1994, the patients without chelation after blood transfusions suffer more and have less life expectancy than the ones who get chelation therapy. Based on the studies by Thalassemia International Federation,2004 and Gatterman guidelines on iron chelation therapy 2007, it is seen that adequacy of transfusion is achieved when haemoglobin levels will reach above 9gm/dl and serum ferritin should be below 1000ng/ml after the first 10-20 transfusion or in the child of 2-3 yrs of age.[3]

While in our study 56.4% of the patients acquired Hb levels below 9gm/dl and only 6.4% of the study population has ferritin levels below 1000ng/dl which shows complete adequacy is not achieved. Compared to another study conducted by Shah et al on the effectiveness of transfusion programs in thalassemia major patients receiving multiple blood transfusions at a transfusion centre in western India showed that only 6.3% of the patients receiving multiple blood transfusions have the average ferritin level below 1000ng/ml which is equal to our study. The study reveals that 53.5% of study subjects have haemoglobin less than 9gm/dl which is slightly less than our study.[19]

CONCLUSION

Nearly 56.4% of the patients are undertransfused as their haemoglobin levels didn't reach the expected value. To safeguard the health of the transfusion recipient, blood should be obtained from carefully selected regular voluntary, non-renumerated donors and should be collected, processed, stored and distributed in the context of deducted, quality-assured blood transfusion centres. For effective transfusion therapy-

- Patients with beta-thalassemia major should receive leukoreduced packed red cells with minimum haemoglobin content of 40gm.
- Use leukoreduced packed red cells. Pre-storage filtration should be done. Blood bank pre-transfusion or bedside filtration are acceptable alternatives.
- Washed red cells for patients who have severe allergic reactions.
- Use red cells stored in CPD-A as fresh as possible (less than one week old) and in additive solutions for less than 2 weeks.
- Transfuse every 2-5 weeks maintaining pre-transfusion Hb above 9-10.5gm/dl but higher levels (11-12gm/dl) may be necessary for patients with heart complications.
- Keep post-transfusion not higher than 14-15gm/dl and should be monitored occasionally to allow assessment of the rate of fall in the haemoglobin level between transfusions in evaluating the effects of changes in the transfusion regime, the degree of hypersplenism or unexplained changes in response to transfusion.

An adequate regime for chelation therapy is required as 93.6% of the study population has high iron overload. The primary goal of chelation therapy is to maintain safe levels of body iron at all times. Unfortunately, once iron overload has accumulated removal of storage iron is slow and inefficient because only a small proportion of body iron is available for chelation at any given time.

Looking for a high prevalence of HCV transmission proper screening of the blood before transfusion can help in reducing these transfusion-transmitted infections. For its effective screening, prenatal testing is to be performed in the early days of childhood to prevent any more worsening of the condition. Non-invasive prenatal diagnosis is a recently developed technique for the detection of defective inherited genes. There is a strong need to create awareness among patients about the consequences of iron overload in their bodies. The high level of serum ferritin of beta thalassaemia major patients noted in this study supports the rationale for regular follow-up of transfusion-dependent thalassaemic patients concerning iron overload to ensure proper management of iron overload-associated complications. Proper chelation of iron overload could improve the quality of life of these patients. The problems of poverty, low education level and inadequate provision of health care are the main stumbling blocks in the effective treatment of iron overload in thalassaemic patients which is the main cause of morbidity and mortality in thalassaemia major.

HIV, HBV, and HCV infections are prevalent TTI'S among multiply transfused patients of beta thalassemia major and remain a major health problem for these patients. The implementation of measures such as donor education programs, standards for donor selection criteria and

improved serological screening protocols, paralleled the decline in the prevalence of TTI especially of HCV should be used to curtail the transmission.

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