International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

Original Research Article.

Response of Thalidomide in Transfusion Dependent Thalassemia

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ABSTRACT

Background: Thalassemia is the most common single gene hereditary disease worldwide. Hb E-β Thalassemia is the commonest severe form of thalassemia in south-east Asia including Bangladesh. The clinical benefit of increased Hb-F in thalassemia treatment is well established which act by decreasing the imbalance between α & non α chains and the consequent reduction of haemolysis. Recent study showed outstanding results on haemoglobin level and transfusion requirement in thalassemia patients treated with thalidomide.

Objective: Aims of our study is to explore the effectiveness of thalidomide in the treatment of thalassemia to improve the haemoglobin level, reduce blood transfusion, to avoid adverse reactions caused by transfusion and to monitor any adverse reaction by therapy.

Method: In this quasi-experimental study 50 patients >12 years old attended in Thalassemia clinic, Department of Haematology, Dhaka Medical College & Hospital, Dhaka was recorded as study cases. All relevant collected prospectively from patients and recorded in prescribed form (Data collection sheet). After full explanation, informed written consent were taken from the selected patients informing the details of the purpose of the study. Data processed and analyzed with the help of computer programme SPSS (Statistical package for social sciences) win version 25 & presented in the form of tables, graphs & chart.

Result: In study cases it was found that there was significant increment of Hb, Hematocrit, HbF% and improvement of performance status 6months after thalidomide therapy (mean 6.36 ±0.78 vs 7.49±0.59, 19.89±2.57 vs 25.88±2.47, 23.03±14.61% vs 39.42±13.31% and 2.24±0.43 vs 1.50±0.54; respectively; all p <0.001). It also revealed that after 6 months of thalidomide therapy there were significant reduction of transfusion requirement, spleen size, nRBC count, Serum LDH, Serum Bilirubin (total) and Serum ferritin (100.06±27.2 vs 54.48±18.34 ml/kg/year, 12.3±6.73 vs 9.28±5.26 cm, 42.28±61.02 vs 16.96±30.14 nRBC/100 WBC, 502.60±124.54 vs 413.28±152.43 U/L, 3.00±1.36 vs 2.12±0.78 mg/dl, 2235.3±2225.6 vs 1574.9±1540.7; respectively, all p<0.001).

Conclusion: In transfusion dependent thalassemia patients, thalidomide is an effective therapy in respect of improving features of extra medullary haemopoiesis and haematologic parameters. It was also found that thalidomide also significantly reduces features of haemolysis without any significant adverse effect.

Keywords: Thalassemia, Thalidomide, Haemopoiesis, Haematologic.

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Article History:

Received: 04-12-2021, **Revised:** 02-01-2022, **Accepted:** 31-01-2022

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2022.8.1.004	

INTRODUCTION

Thalassemias are a group of autosomal recessive disorder and the most common single gene disorder worldwide with a wide geographical variation in incidence. It was first recognized by Cooley & Ley in 1925 as a form of severe anaemia associated with splenomegaly and bone changes in children.

It is presumed that approximately 6000 thalassemic children are born each year in Bangladesh but most of the population is unaware of this hereditary disease, only a few cases are diagnosed. Bangladesh having of over 160 million, there is no national data about the number of thalassemia patient in the country. Tahura et al (2016) estimated that existing thalassemic patients in Bangladesh is about 1 lac and suspected total number of β thalassemia major and Hb E- β thalassemia born around1040 and 6443 per year respectively[1].

Hossain et al (2017) found Hb E - β thalassemia is 67% in a case study in thalassemic patients in Dhaka[2]. In another study conducted in Dinajpur Medical college Hospital, Tahura et al (2016) observed that among 60 patients, Hb E trait was 41.67%, Hb-E disease was 30%, Hb-E - β thalassemia and β thalassemia trait was 23.33% and 3.33% respectably[1].

A conservative WHO report has shown that 3% of population carries β thalassemia and 4% carries Hb-E in Bangladesh. But according to Tahura et al (2016) carrier status of Hb-E is 6.1% and as high as 41.7% in tribial school children in Bangladesh[1]. Farhana, Nahar & Choudhury (2009) found 17.39% Hb E trait and 13.04% Hb E disease in their study in Bangladesh Institute of Rehabilitation in Diabetes, Endocrine and Metabolic disorder (BIRDEM). So, it is explicable that thalassemia is an emerging health burden for our country[3].

Thalassemia is a haemoglobinopathy caused by production of reduced amount of globin chains. Two major categories are the & β thalassemias. Functionally some thalassemia mutations cause a complete absence of globin chain synthesis called α^o or β^o thalassemias. The vast majority of β thalassemia mutations are point mutations (single base substitutions) & small insertions and deletions of one or two base pairs and may involve any step of globin chain synthesis- transcription, translation and post translational stability.

In β thalassemia imbalance of globin chain production leads to excess α chains. The free α globin chains are highly unstable and precipitate in erythroid precursors in bone marrow causing intracellular inclusions that interfere with RBC maturation. There is variable degree of intramedullary destruction of erythroid precursors (Ineffective erythropoiesis). Those RBC that mature and enter circulation contain α chain inclusions that interfere with their passage through microcirculation, particularly spleen causing haemolysis.

Thalidomide recently has shown novel achievement as haemoglobin F inducer. It is thought to be effective in transfusion dependent thalassemia patients. It has recently been demonstrated that Thalidomide induce HbF by epigenetic mechanism. So, thalidomide may be potent treatment option in thalassemia.

OBJECTIVE

General Objective:

To evaluate the Response of Thalidomide in Transfusion Dependent Thalassemia

Specific Objectives:

- To diagnose Thalassemia by clinical features, CBC, PBF and Hb Electrophoresis results.
- To assess clinical response by monitoring quality of life (ECOG performance status) transfusion requirement and splenomegaly.
- To assess laboratory response by Haemoglobin, Haematocrit, reticulocyte count, nucleated red blood cell count, Serum Ferritin and Haemoglobin F, Serum bilirubin, Serum LDH 3 monthly.
- To monitor closely for any adverse drug reactions
- Monitoring will be done in screening visit, Then 3 monthly for next 12 months.

METHODOLOGY

Study Design

Quasi-Experimental study (Clinical trial).

Place of Study

Department of Haematology, Dhaka Medical College & Hospital, Dhaka.

Study Period

This study was conducted from July 2018 to June 2019 for duration of 12 months.

Study Population

All adult transfusion dependent thalassemia patients receiving treatment in Department of Haematology, Dhaka Medical College & Hospital.

Sampling Method

Purposive sampling. All patients who are fulfilling the inclusion and exclusion criteria are to be studied.

Sample Size and Statistical Basis of it:

As the study will be conducted within 12 months and few patients will meet inclusion and exclusion criterias, the sample size will be reduced to 50.

So, the sample size will be at least 50.

Selection Criteria

Inclusion Criteria:

1. Both transfusion dependent E/Beta thalassemia and Thalassemia Major Patients.
2. Both sex
3. Age: More than 12 years.
4. Patients clinical parameter and transfusion requirement not improving with regular transfusion only.
5. Sign an informed consent agreeing to the experimental study
6. Non-pregnant women.

Exclusion Criteria:

1. Patients with age group below 12 years.
2. Women during pregnancy, breastfeeding or those of child bearing age who do not want to take contraceptive measures.
3. Patients had comorbidities like severe heart or lung diseases, liver dysfunction, cerebrovascular, cardiovascular, liver, kidney tumours or other serious primary diseases.
4. History of hypersensitivity to thalidomide.
5. Patients with any mental problems.
6. Patients had a history of venous or arterial thrombosis.

Procedure of Collecting Data:

Diagnosis of Thalassemia by

1. Taking clinical information in prescribed Data collection sheet.
2. Estimation of Complete Blood Count (CBC) in the department of Hematology of DMCH by Sysmex XE-5000 Automated hematology analyzer.
3. Peripheral blood: Examination of peripheral blood film under light microscopy after Leishman stain and checked by hematologist.
4. Haemoglobin Electrophoresis by Capillary Method.

Procedure of Data Analysis:

All data were tabulated by using Microsoft Excel. All statistical analysis done by IBM SPSS (Statistical Package for the Social Science) Statistics 25 software package. Distribution for data was determined by SPSS 25 software package. Paired t-test, Unpaired test, McNemar's test, Pearson correlation test were calculated by SPSS 25 software package.

RESULTS

Table I shows the distribution of the study patients by age. It was observed that almost two thirds (60.0%) of patients belonged to age ≤20 years. The mean age was 19.9±7.32 years with ranged from 12 to 37 years.

Table II shows the distribution of the study patients by sex. It was observed that more than two thirds (68.0%) of patients were male and 16(32.0%) were female.

Table III shows the distribution of the study patients by type of thalassemia. It was observed that majority (96.0%) patients had E-Beta thalassemia and 2(4.0%) Homozygous beta thalassemia.

Figure 1 shows the distribution of the study patients by splenectomy status. It was observed that more than three fourth (80.0%) of patients was not splenectomized and 10(20.0%) was splenectomized.

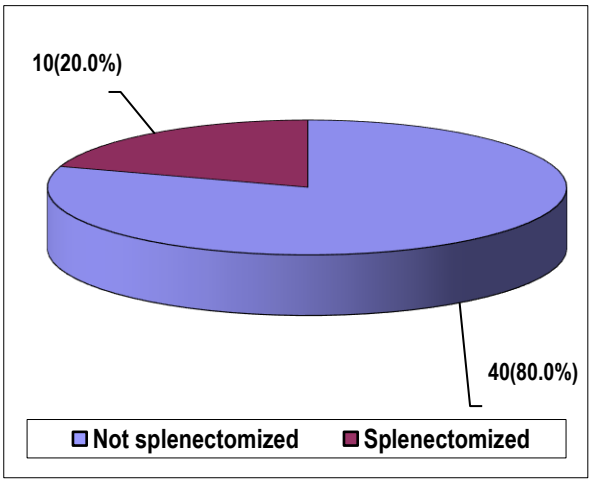

Fig 1: Distribution of study patients by splenectomy status

Table I: Distribution of the study patients by age (n=50)

Age (in years)	Number of patients	Percentage
≤20	30	60.0
21-30	15	30.0
31-40	5	10.0
Mean±SD	19.9±7.32	
Range(min-max)	12-37	

Table II: Distribution of the study patients by sex (n=50)

Sex	Number of patients	Percentage
Male	34	68.0
Female	16	32.0

Table III: Distribution of the study patients by type of thalassemia (n=50)

Type of thalassemia	Number of patients	Percentage
E-Beta Thalassemia	48	96.0
Homozygous beta thalassemia	2	4.0

Table IV: Correlations Between HbF%, HCT, Spleen size, Transfusion requirement before thalidomide, S. Ferritin, nRBC/100 WBC, S. LDH and S. Bilirubin (T).

Correlations Between	Correlations	p value
HbF% at 1st presentation VS HbF% 6m after thalidomide	0.752	0.001
Steady state Hb (gm/dl) VS Hb 3m after thalidomide (gm/dl)	0.493	0.001
Steady state Hb (gm/dl) VS Hb 6m after thalidomide (gm/dl)	0.164	0.255
HCT before thalidomide (%) VS HCT 6m after thalidomide (%)	0.371	0.001
Spleen size before thalidomide (cm) VS Spleen size 6m after thalidomide (cm)	0.903	0.001
Transfusion reaction before thalidomide (ml/kg/year) VS Transfusion requirement 6m after thalidomide (ml/kg/year)	0.833	0.001
S. Ferritin before thalidomide (ng/ml) VS S. Ferritin 6m after thalidomide (ng/ml)	0.874	0.001
nRBC/100 WBC before thalidomide VS nRBC/100 WBC 6m after thalidomide	0.860	0.001
S. LDH before thalidomide (U/L) VS S. LDH 6m after thalidomide (U/L)	0.661	0.001
S. Bilirubin (T) before thalidomide (mg/dl) VS S. Bilirubin (T) 6m after thalidomide (mg/dl)	0.696	0.001

Table V: Thalidomide effect after 3 months and 6 months in transfusion dependent thalassemia

At 3 months	After 6 months			Row total
	Main responders Hb increments >2 g/dl	Minor responders Hb increments 1-2 g/dl	Non responders <1 g/dl	
Main responders	6	0	0	6
Minor responders	10	7	3	20
Non responders	2	15	7	24
Column total	18	22	10	50

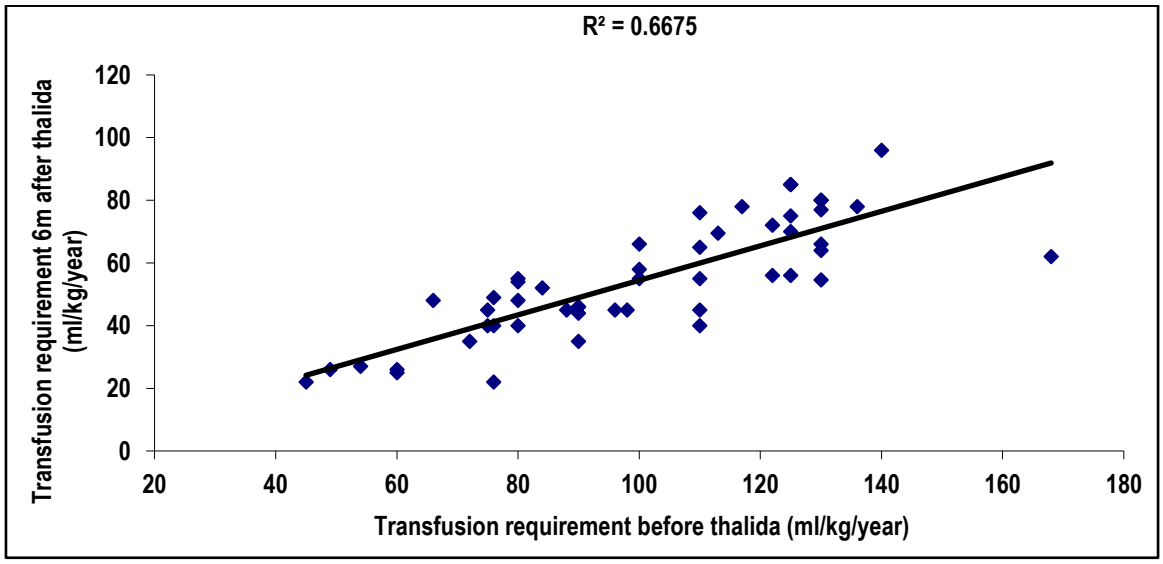

Fig 2: Scatter diagram showing positive significant correlation (r=0.833; p=0.001) between transfusion requirement before thalidomide (ml/kg/year) and transfusion requirement 6m after thalidomide (ml/kg/year).

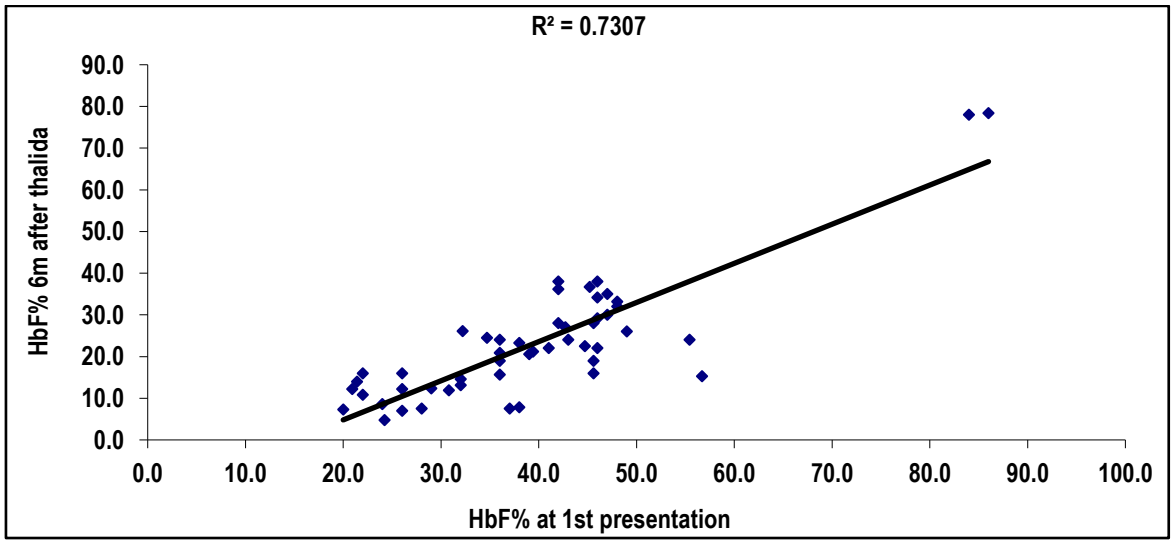

Fig 3: Scatter diagram showing positive significant correlation (r=0.752; p=0.001) between HbF% at 1st presentation and HbF% 6m after thalidomide.

DISCUSSION

The thalassemia syndromes are a group of disorders that result from decreased or absent synthesis of one or more of the globin subunits that form the normal human haemoglobins (Hbs). According to the most current Bulletin of the World Health Organization, inheritance of thalassemic mutations represents a significant public health problem in a majority of nations (71% of 229 countries)[4].

Thalidomide, an immunomodulatory agent has been shown emerging role in fetal haemoglobin induction. A lot of study suggests that in transfusion dependent thalassemia thalidomide increases Hb and improves hematological parameters.

This study was quasi-experimental nonrandomized (time series design). In this study 50 mg fixed daily dose of oral thalidomide was given to each study case and effect of thalidomide observed 3 monthly. The study was conducted in Department of Haematology, Dhaka Medical College and Hospital, Dhaka.

Study population was selected according to certain criteria as describe early. This study included only >12 years age group as some studies were conducted in this age group only e.g: Masera et al. (2010), Jiangming chen et al. (2017) Ren et al. (2018), Ramanan and Kelkar (2017).[5-7] Pediatric age group was not included here.

Main purpose of this study was to deal with variable like Hb increment, HbF% improvement, haematocrit rise, improvement of features of extramedullary haemopoiesis, depicted as performance status and spleen size changes following thalidomide therapy. The study also revealed the effect of thalidomide over reduction of extravascular hemolysis parameters depicted as changes in nRBC count S. bilirubin, S. LDH, S. Ferritin. This study also calculated distribution of age and sex of the participants. As this was not designed to see distribution of age or sex, result of this variable may be inconsistent with previous study.

Among the 50 participants 68.0% were male and 32.0% were female. The participants were divided in three age group, the mean age was 19.9±7.32 years with ranged from 12 to 37 years.

In non splenectomized patients change in Hb value after 3 months of thalidomide therapy from a mean of 6.44±0.67 to 7.57±0.58 gm/dl. However, in the same group of patients 6 months after thalidomide therapy mean Hb was 8.41 ± 0.76 gm/dl[8].

In splenectomized patients change in Hb value after 3 months of thalidomide therapy from a mean of 6.03±1.09 gm/dl to 7.18±0.57 gm/dl. However, in the same group of patients 6 months after thalidomide therapy mean Hb was 7.82±0.81 gm/dl. The mean difference of Hb at 3m after thalidomide was higher in non splenectomized compared to the value of splenectomized cases, but the difference was statistically not significant[9]. However, the mean difference of Hb at 6m after thalidomide was significantly higher in non splenectomized patients compared to splenectomized cases.

The mean HbF, Hb and HCT were significantly (p<0.05) increased at 6m after thalidomide with compared to the value at presentation (before thalidomide).

The mean spleen size was 12.30±±6.73 cm before thalidomide and 9.28±5.26 cm at 6m after thalidomide. The mean transfusion requirement before thalidomide was 100.06±27.2 (ml/kg/year) and 6m after thalidomide was 54.48±18.34 (ml/kg/year). The mean S. Ferritin before thalidomide was 2235.3±2225.6 (ng/ml) and 6m after thalidomide was 1574.9±1540.7 (ng/ml). The mean nRBC/100 WBC before thalidomide was 42.28±61.02 and 6m after thalidomide was 16.96±30.14. The mean S. LDH before thalidomide was 502.60±124.54 (U/L) and 6m after thalidomide was 413.28±152.43 (U/L). The mean S. Bilirubin (T) before thalidomide was 3.00±1.36 (gm/dl) and 6m after thalidomide was 2.12±0.78 (mg/dl). The difference was statistically significant (p<0.05)[10]. Hypothesis testing with McNemar test analysis showed p value <0.001. P value ≤0.05 was considered significant for this study. So, Null hypothesis was rejected. Thalidomide significantly improves haematological parameters in transfusion dependent thalassemia. In our study we also found significant reduction of transfusion requirement, spleen size, serum ferritin, serum LDH, Serum Bilirubin and nRBC count 6 months after thalidomide therapy (p≤0.01).

Our study end point was to assess Hb increment, and cases are divided into main responders, minor responders and non-responders according to Hb increment status. Analysis showed at 3 months of Thalidomide therapy main responders found 6, minor responder 20 and non-responders 24. After 6 months of Thalidomide therapy main responders found 18, minor responder 22 and non-responders 10. The null hypothesis of thalidomide is a non-effective therapy in transfusion dependent thalassemia. From the McNemar test statistic p value reached <0.001. p value ≤ 0.05 was considered significant for this study. Thus, the test provides strong evidence to reject the null hypothesis of no thalidomide effect. This study showed strong positive correlation between thalidomide therapy and different clinical and haematological parameters (r=0.7-1; p<0.001) of transfusion dependent thalassemia patients. p value ≤ 0.05 was considered significant for this study. So, Ha was accepted.

CONCLUSION

Transfusion dependent thalassemia is a major health burden in respect to transfusion hemosiderosis, extramedullary hemopoiesis and complication of anemia. Though thalidomide cannot cure the basic genetic defect of thalassemia it can significantly reduce globin chain imbalance with resultant improved phenotypic parameters, e.g: all hematological parameters, features of EMH and extravascular hemolysis. So, in our socioeconomic perspective thalidomide is a promising and time demanding therapy in transfusion dependent thalassemia. In Bangladesh, malnutrition is frequent among children with congenital cardiac defects which increases risk of morbidity is related with prolonged mechanical ventilation and ICU stays. To minimize potentially harmful effects, the health care system should be able to screen and identify these individuals early on.

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Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Md. Ashikuzzaman. Response of Thalidomide in Transfusion Dependent Thalassemia. Int J Med Res Prof. 2022 Jan; 8(1): 15-19.
DOI:10.21276/ijmrp.2022.8.1.004