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Haematology

Response of Thalidomide in Spleen Size Reduction of Transfusion Dependent Thalassemia

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Abstract **Original Research Article**

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 β& non- β chains and the consequent reduction of haemolysis. Recent study showed outstanding results on haemoglobin level and transfusion requirement in thalassemia patients treated with thalidomide. ***Objectives: Aims of our study is to evaluation of thalidomide in spleen size reduction of transfusion dependent thalassemia. ***Methods and Materials:*** In this quasi-experimental study 50 patients >12 years old attended in Thalassemia clinic, Department of Haematology, Dhaka Medical College & Hospital, Dhaka were 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. ***Results*:** In study cases it was found that there were 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 reveledthat 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±30.14nRBC/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 haemopoiesisand haematologic parameters. It was also found that thalidomide also significantly reduce features ofhaemolysis without any significant adverse effect.

Key words: Thalassemias, Haemoglobin increment, Thalidomide effects.

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INTRODUCTION

Thalassemias are a set of autosomal recessive disorders with substantial geographical variation in prevalence. Cooley & Ley identified it as a severe anemia with splenomegaly and bone abnormalities in children in 1925. Every year, roughly 6000 thalassemic babies are born in Bangladesh, although most people are uninformed of the disease, and only a few are diagnosed. Despite a population of over 160 million, there is no official statistics on thalassemia patients. In a study estimated the number of thalassemic patients in Bangladesh to be around 1 lac, with 1040 and 6443 thalassemia major and Hb E- thalassemia born per year [1]. In a case study of thalassemic patients in Dhaka, Hossain *et al.* Tahura *et al*. (2016) found that among 60 patients at Dinajpur Medical College Hospital, Hb-E trait was 41.67 percent, Hb-E disease was 30%, and Hb-E - thalassemia was 23.33 percent and 3.33 percent, respectively. According to a WHO report, 3% of Bangladeshis have thalassemia and 4% have Hb-E. According to Tahura *et al.* (2016), Hb-E carrier status ranges from 6.1 to 41.7 percent among Bangladeshi tribial school children. In their study at the Bangladesh Institute of Rehabilitation in Diabetes, Endocrine, and Metabolic Disorder, Farh ana, Nahar, and Choudhury identified 17.39% Hb E trait and 13.04% Hb E disease (BIRDEM). Thus, thalassemia is a growing health issue in our country [2].

Thalassemia is a haemoglobinopathy caused by diminished globin chain synthesis. Three types of thalassemias exist. There are thalassemia mutations that prevent globin chain production completely. These mutations can affect every phase of globin chain production, including transcription, translation, and post-translational stability [3]. Excess globin chains result from thalassemia. They are highly unstable and cause intracellular inclusions that prevent RBC maturation. Intramedullary degradation of erythroid precursors varies (Ineffective erythropoiesis). RBC that develops and enter circulation includes chain inclusions that obstruct microcirculation, producing haemolysis. Thalidomide recently achieved an unique haemoglobin F inducer feat. It may help transfusion-dependent thalassemia patients. Thalidomide induces HbF via epigenetic mechanism [4]. Talalisomide may be effective in thylasema treatment. Efficacy and safety of thalidomide in thalassemia have been extensively studied in international publications. Thalidomide was found to be more effective than standard therapy, iron chelation, and even hydroxyurea. In these experiments, thalidomide was more powerful HbF inducer, more convenient, and less expensive. But no such study on thalidomide has been done in our nation. Thalassemia is endemic in our country, and the majority is poor. They struggle with regular blood transfusions and chelation. If we can show thalidomide's efficacy, it will benefit our thalassemia sufferers [5].

OBJECTIVES

Evaluation of thalidomide in spleen size reduction of transfusion dependent thalassemia

METHODS AND MATERIALS

This Quasi-Experimental study (Clinical trial) study was conducted in the department of Haematology, Dhaka Medical College & Hospital, Dhaka. This study was conducted from July 2018 to June 2019 for duration of 12 months. 50 adult transfusion dependent thalassemia patients receiving treatment in Department of Haematology, Dhaka Medical College & Hospital selected as a sample population through following purposive sampling method.

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.

DATA COLLECTION AND ANALYSIS

All the clinical information collected in a prescribed data sheet. 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-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 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.

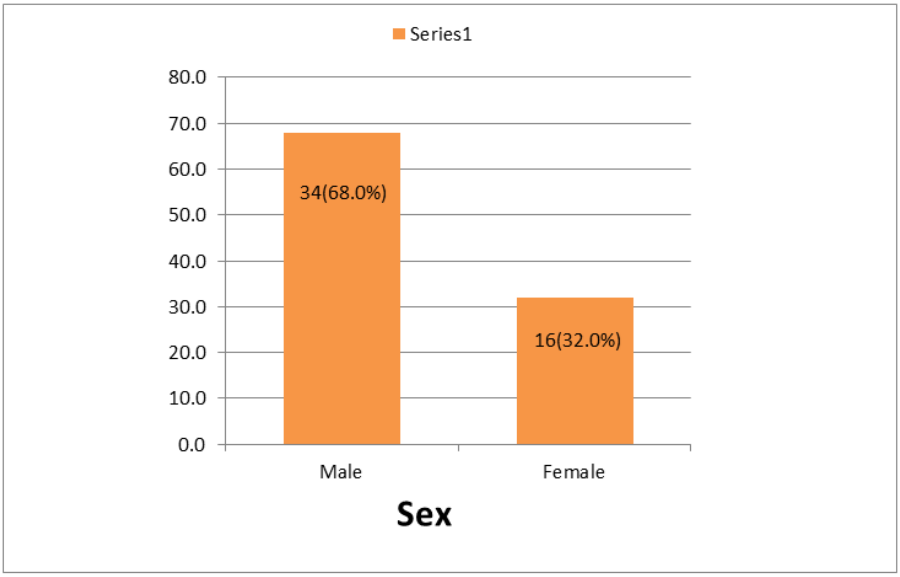

Fig-1: Gender Distribution of the patients

Figure 2 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.

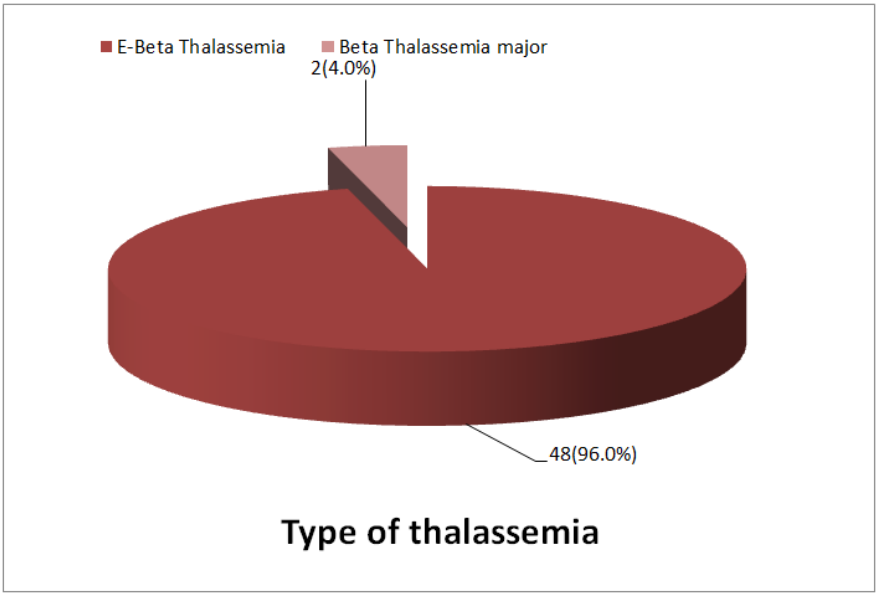

Fig-2: Type of Thalassemia

Table II shows the distribution of the study patients by splenectomy status. It was observed that more than three fourth (80.0%) of patients wasnot splenectomized and 10(20.0%) was splenectomized.

Table-II: Distribution of the study patients by type of splenectomystatus (n=50)

Splenectomy status	Number of patients	Percentage
Not splenectomized	40	80.0%
Splenectomized	10	20.0%

The mean steady state Hb was 6.44±0.67 % in non splenectomized and 6.03±1.09 % in splenectomized patients. The mean Hb at 3m after thalidomide was 7.57±0.58 % in non splenectomized and 7.18±0.57 % in splenectomized. The mean Hb at 6m after thalidomide was 8.41±0.76% in non splenectomized and 7.82±0.81% in splenectomized. 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. Howeverthe mean difference of Hb at 6m after thalidomide was significantly higher in non splenectomizedpatients compared to splenectomized cases.

Table-III: Comparison of Hb value in between splenectomized and non splenectomizedstudy populations (n=50)

Hb %	Splenectomy				P value
	Not done (n=40)		Done (n=10)		
	Mean	±SD	Mean	±SD	
Steady state Hb	6.44	± 0.67	6.03	±1.09	0.137^{ns}
Ranger (min-max)	5.0	-7.7	4.4	-7.6	
3m after thalidomide	7.57	±0.58	7.18	±0.57	0.062^{ns}
Ranger (min-max)	6.4	-9.1	6.0	-7.8	
6m after thalidomide	8.41	±0.76	7.82	±0.81	0.038^{s}
Ranger (min-max)	6.8	-11.1	7.0	-9.1	

s=significant ns=not significant
p value reached from Unpaired t-test

Table IV shows the distribution of the study patients by Hb increments status. It was observed that 6(12.0%) were main responders, 20(40.0%) minor responders and 24(48.0%) patients were non responders.

Table IV: Distribution of the study patients by Hb increment status 3m after thalidomide (n=50)

Hb (gm/dl)	Number of patients	Percentage
Main responders: Hb increments >2 g/dl	6	12.0%
Minor responders: Hb increments 1-2 g/dl,	20	40.0%
Non responders <1 g/dl	24	48.0%

Table V shows the distribution of the study patients by Hb increments status. It was observed that only 2(4.0%) were main responders, 18(36.0%) minor responders and 30(60.0%) patients were non responders.

Table-V: Distribution of the study patients by Hb increment status from 3m-6m after thalidomide (n=50)

Hb (gm/dl)	Number of patients	Percentage
Main responders: Hb increments >2 g/dl	2	4.0
Minor responders: Hb increments 1-2 g/dl,	18	36.0
Non responders <1 g/dl	30	60.0

Table VI shows the distribution of the study patients by Hb increments status. It was observed that 18(36.0%) were main responders, 22(44.0%) minor responders and 11(22.0%) patients were non responders.

Table-VI: Distribution of the study patients by Hb increment status 6m after thalidomide (n=50)

Hb (gm/dl)	Number of patients	Percentage
Main responders: Hb increments >2 g/dl	18	36.0
Minor responders: Hb increments 1-2 g/dl,	22	44.0
Non responders <1 g/dl	11	22.0

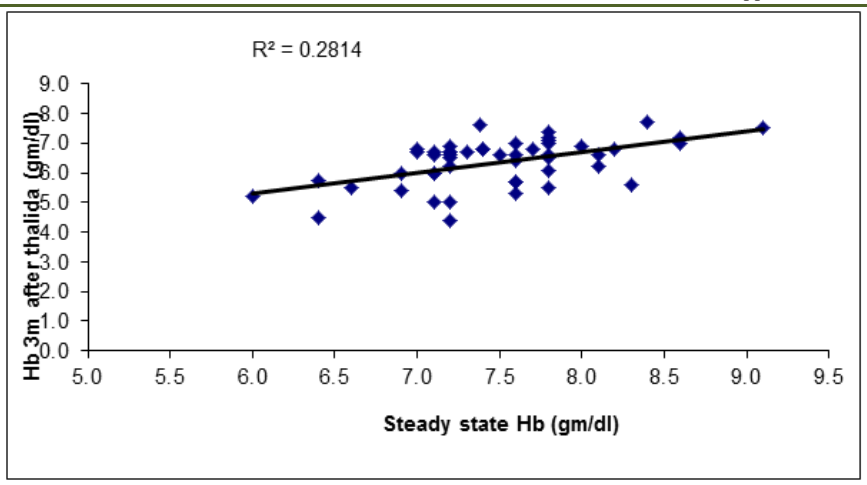

Fig-3: Scatter diagram showing positive significant correlation (r=0.493; p=0.001) between steady state Hb (gm/dl) and Hb 3m after thalidomide (gm/dl).

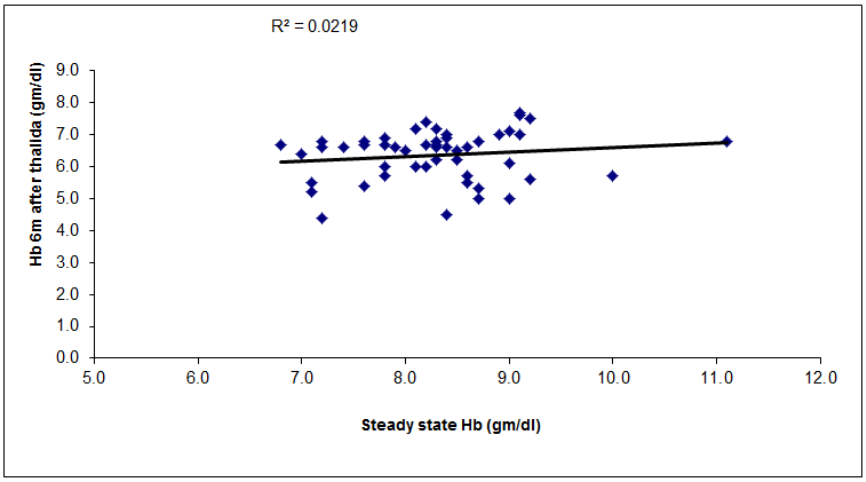

Fig-4: Scatter diagram showing positive not significant correlation (r=0.164; p=0.255) between steady state Hb (gm/dl) and Hb 6m after thalidomide (gm/dl).

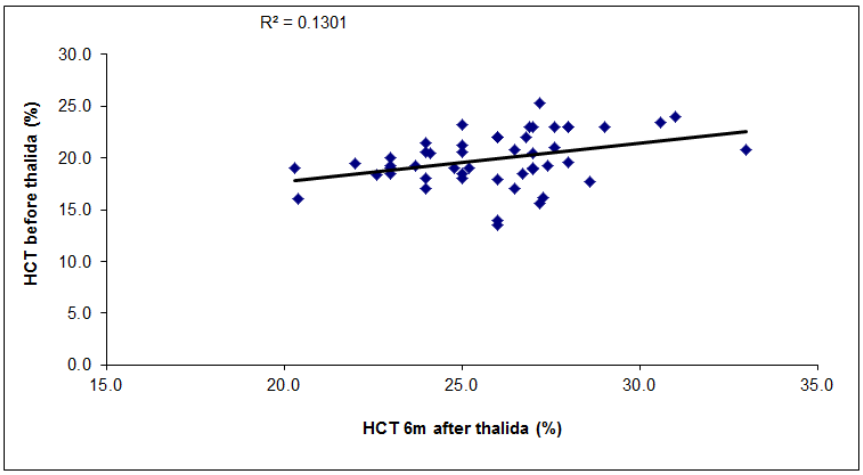

Fig-5: Scatter diagram showing positive significant correlation (r=0.341;p=0.001) between HCT 6m after thalidomide (%) and HCT before thalidomide (%).

Table-VII: 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

DISCUSSION

Transfusion dependent thalassemia is a major health burden in respect of transfusion haemosiderosis, high cost of chelation therapy and infectious complications. For patients with homozygous β-thalassemia, an increased γ-globin chainproduction would result in a more balanced α/non-α ratio and an amelioration ofthe severity of the anemia. In fact, γ-chains can neutralize the harmful excess ofα-chains and allow a better survival of erythroid precursors in the bone marrowand of the red cells in the peripheral blood. Effective procedures to enhance redcell production could reduce or even eliminate the need for transfusions andwould represent a major advance in the treatment of homozygous β-thalassemia [6].

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.

A few randomized trails of thalidomide therapy in thalassemia patients demonstrated a consistent increment of Hb and other haematologicalparameter following thalidomide therapy.

This study was designed to analyze efficacy of thalidomide in transfusion dependent thalassemia in respect of Hb and haematocrit changes, improvement of features of extramedullary haemopoiesis and haemolysis.

This study was quasi-experimental non randomized (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 study were conducted in this age group [7-10]. Pediatric age group was not included here.

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.

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. However, the mean difference of Hb at 6m after thalidomide was significantly higher in non splenectomized patients compared to splenectomized cases.

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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 an promising and time demanding therapy in transfusion dependent thalassemia.

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