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Effects of thalidomide in transfusion-dependent beta-thalassemia patients

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Abstract

Backgrounds: Beta thalassemia constitutes inherited disorders of hemoglobin (Hb) synthesis caused by decreased synthesis of β-globin chains and relative overproduction of α-globin chains, causing cell membrane damage, which plays a key role in ineffective erythropoiesis and peripheral hemolysis. Thalidomide, a fetal Hb inducer, shows significant effects in increasing Hb as well as transfusion requirements. This study aimed to evaluate the effects of thalidomide in transfusion-dependent beta-thalassemia patients.

Methods: The prospective study was conducted at the Department of Pediatric Hematology and Oncology in collaboration with the Department of Hematology at Sir Salimullah Medical College Mitford Hospital over 1 year, from November 2022 to October 2023. A sample size of 54 with selection criteria included individuals with diagnosed cases of beta thalassemia who were transfusion-dependent. Thalidomide was given at 5 mg/kg/day to all age groups, along with aspirin at 3 mg/kg/day coverage, in addition to conventional therapy. Then, four monthly follow-ups were done for 1 year.

Result: Thalidomide leads to an increase in mean Hb levels from 7.06 ± 0.99 g/dL to 9.33 ± 1.16 g/dL ($P < 0.001$) after 1 year of treatment. The mean number of blood transfusions reduced from 10.98 ± 1.41/year to 10.31 ± 1.36 ($P < 0.001$) after 1 year of treatment.

Conclusion: The study revealed that thalidomide treatment led to a substantial increase in Hb levels as well as a notable decrease in transfusion frequency.

Keywords: Beta thalassemia, blood transfusion, hemoglobin, thalidomide.

Introduction

Beta thalassemia is an autosomal recessive inherited disorder of hemoglobin (Hb) due to a defect involving the beta-globin gene. The absence or severely impaired production of β-globulin in β-thalassemia results in a relative excess of α-globulin chains forming insoluble aggregates in erythrocyte precursors, leading to ineffective erythropoiesis and shortened Red cell survival.[1] At present, beta thalassemia is classified according to the clinical severity and transfusion requirements into transfusion-dependent and non-transfusion-dependent. Treatment relies on controlling the chronic hemolysis that is associated with both symptomatic anemia and organ dysfunction in these disorders. Chronic transfusion therapy, iron chelation, hydroxyurea therapy, and splenectomy

are often employed.[2] Although various options for the management of thalassemia are available currently, there are limitations with the existing therapies; hence, there is an unmet need for newer agents. Inducers of fetal hemoglobin (HbF), such as hydroxyurea and histone deacetylase inhibitors, are effective in improving Hb levels by higher production of γ-globin which lowers the imbalance between β and non-β chains and thus reduces hemolysis.[3] Thalidomide, an HbF inducer, also has an immunomodulatory agent with antiangiogenic properties and has been used in severe thalassemia cases after various immunomodulatory approach failures.[3] Previous studies have also shown that thalidomide is effective in the pediatric population as well as in adults.[4,5] In a study conducted in India, thalidomide resulted in a major (51.3%) and moderate response (32.4%) in children with transfusion-dependent thalassemia (TDT) with satisfactory adverse side effects.[6] The effects of thalidomide are attributed to its suppression of NF-κB activation induced by inflammatory cytokines, such as tumor necrosis factor-alpha, vascular endothelial growth factor, and prostaglandin E2. This suppression is associated with an increased release of reactive oxygen species, which can activate the P38 MAPK pathway, ultimately leading to elevated HbF levels.[5] The major side effects of thalidomide were reported as somnolence, constipation, deep venous thrombosis, and teratogenicity when used during pregnancy. Even though the mechanisms by which thalidomide increases erythropoiesis and induces γ-globin gene expression and HbF production have been described, clinical experience with thalidomide in transfusion-dependent β-thalassemia in the pediatric population is rare in our country. In Bangladesh, one study has been published regarding the outcome of treatment with thalidomide in TDT patients.[7] This study will help to evaluate the effects of thalidomide increasing Hb to reduce the frequency of blood transfusion in transfusion-dependent beta-thalassemia children.

Methods

This prospective longitudinal study was conducted by the Department of Pediatrics, Pediatric Hematology, and Oncology with the collaboration of the Department of Hematology, Sir Salimullah Medical College Mitford Hospital, from November 2022 to October 2023 to evaluate the effects of thalidomide on the increase in Hb, to reduce the frequency of blood transfusion in transfusion-dependent beta-thalassemia children. Diagnosed cases of transfusion-dependent beta-thalassemia in the age group of 2–15 years were considered in the study population. A total of 54 patients were selected as study subjects by purposive sampling technique. The main outcome variables of the study were the effects of thalidomide treatment on Hb levels and the frequency of blood transfusions in transfusion-dependent β-thalassemia patients. Laboratory investigations, including complete blood count, alanine aminotransferase, serum creatinine, chest X-ray, and echocardiography, were performed. Thalidomide (Thalix brand name: Indian pharmaceutical) was given at 5 mg/kg/day to all age groups, along with aspirin (3 mg/kg/day) coverage, as thalidomide has a thrombotic tendency. Conventional therapy with blood transfusion and iron chelation was continued side by side with thalidomide according to the protocol of the department. All statistical analyses were done using the Statistical Package for Social Science program, version 26 for Windows. Paired t-tests were conducted to evaluate the changes in mean Hb level, before and after treatment with thalidomide and also to compare transfusion frequency before and after treatment. A significance level of $P < 0.05$ was considered statistically significant. Results were expressed by appropriate tables and figures, and analytical discussions were done. After analysis, all data were presented in suitable tables or graphs according to their affinity. The research protocol was approved by the Research Review Committee of the Department of Pediatrics and the Ethical Committee of Sir Salimullah Medical College Mitford Hospital, Dhaka. Informed consent was taken from each patient.

Inclusion criteria

- Diagnosed cases of beta-thalassemia who are transfusion-dependent
- The age group is 2–15 years, both sexes.

Exclusion criteria

- Thalassemic patients who developed disease-related complications such as liver diseases, hypothyroidism, hypoparathyroidism, diabetes mellitus, cardiomyopathies, osteoporosis, and paraparesis
- Any pre-existing chronic conditions such as congenital heart disease, chronic liver disease, or chronic kidney disease
- Those patients who have undergone splenectomy.

Results

Table 1 shows the majority of participants fall within the 5–10 years age group, constituting 53.7% of the total sample, followed by the 2–5 years age group at 35.2%. A smaller proportion, 11.1%, is observed in the 10–15 years age category. The mean age of the participants is calculated at 7.0 ± 3.07 years. Among the participants, male-to-female ratio is calculated at 1.5:1.

Table 2 shows among the patients, the mean age at first diagnosis is recorded as 33.7 ± 11.3 months, and the mean total duration of the disease is reported as 51.21 ± 30.7 months. The mean frequency of blood transfusion per year was 10.98 ± 1.41.

Table 3 shows a comparison of laboratory findings, specifically Hb, before and after 1 year of thalidomide treatment in transfusion-dependent β-thalassemia patients. Before the addition of thalidomide treatment, the mean Hb level was 7.06 ± 0.99 g/dL, which significantly increased to 9.33 ± 1.16 g/dL with thalidomide ($P < 0.001$).

Table 4 presents a comparison of blood transfusion frequencies before and after 12 months of treatment with thalidomide. The mean number of blood transfusions significantly decreased from 10.98 ± 1.41 before treatment per year to 10.31 ± 1.36 after the addition of thalidomide treatment in a year, which indicates a statistically significant difference ($P < 0.001$).

Table 1: Distribution of the study participants according to demographic variables (n=54)

Variables	Number of patients	Percentage
Age group (years)		
2–5	19	35.2
5–10	29	53.7
10–15	6	11.1
Mean±SD	7.0±3.07	
Sex		
Male	32	59.3
Female	22	40.7
Male: female ratio	1.5:1	

SD: Standard deviation

Table 2: Distribution of the study participants according to clinical history (n=54)

Variables	Number of patients	Percentage	Mean±SD
History			
Age at first diagnosis (months)	-	-	33.7±11.3
Total duration of disease (months)	-	-	51.21±30.7
Blood transfusion status			
Regular	42	77.8	-
Irregular	12	22.2	
Frequency of blood transfusion (per year)	-	-	10.98±1.41

SD: Standard deviation

Figure 1 shows the line graph of the serum Hb level in TDT patients from baseline to gradual raising with treatment added with thalidomide. The mean Hb level before the addition of treatment was 7.06 g/dL, which increased gradually after 4 months to 8.13 g/dL, then after 8 months 8.74 g/dL, and to 9.33g/dL after 12 months of treatment.

Figure 2 presents a comparison of mean blood transfusion frequencies before and after 12 months

Table 3: Comparison of hemoglobin level before and after thalidomide treatment in transfusion-dependent β-thalassemia patients (*n*=54)

Laboratory findings	Before treatment (*n*=54), mean±SD	After treatment (*n*=54), mean±SD	*P*
Hb (g/dL)	7.06±0.99	9.33±1.16	<0.001

P-value obtained by Paired *t*-test, $P<0.05$ considered a level of significant. Hb: Hemoglobin, SD: Standard deviation

Table 4: Comparison of mean frequency of blood transfusion before and after thalidomide treatment (*n*=54)

Variable	Before treatment (*n*=54), Mean±SD	After treatment (*n*=54), Mean±SD	*P*
Number of blood transfusions (per year)	10.98±1.41	10.31±1.36	<0.001

P-value obtained by the paired test, $P<0.05$ considered a level of significant. SD: Standard deviation

of treatment with thalidomide. The mean frequency of blood transfusions significantly decreased from 10.98 ± 1.41 before treatment per year to 10.31 ± 1.36 after the addition of thalidomide treatment, which indicates a statistically significant difference ($P < 0.001$).

Discussion

Our study showed all patients are in the 2–15 years age group. Begum *et al.*[7] conducted a study in our country where the age range was 3–24 years. Yassin[4] conducted a study in India on beta-thalassemia patients whose age range was 3–43 years. Jiskani and Menon[5] conducted a study in Pakistan where age all patients were within the 7–12 years age group. These collectively demonstrate that thalidomide is effective in both pediatric and adult populations. The present study reveals a noteworthy increase in mean Hb levels following thalidomide treatment. The mean Hb level before treatment was 7.06 ± 0.99 g/dL, and it significantly increased after 12 months to 9.33 ± 1.16 g/dL after treatment ($P < 0.001$). This improvement

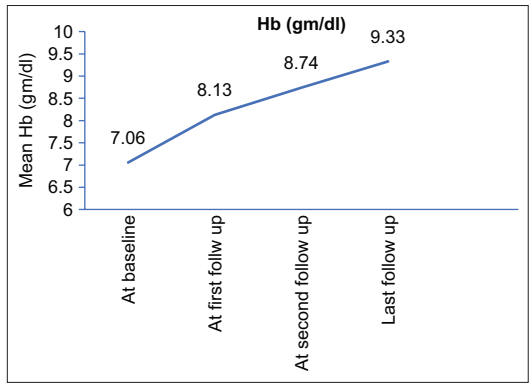

Figure 1: The change of serum hemoglobin level from baseline to last follow-up (4 monthly over 12 months) by thalidomide in transfusion-dependent thalassemia patients

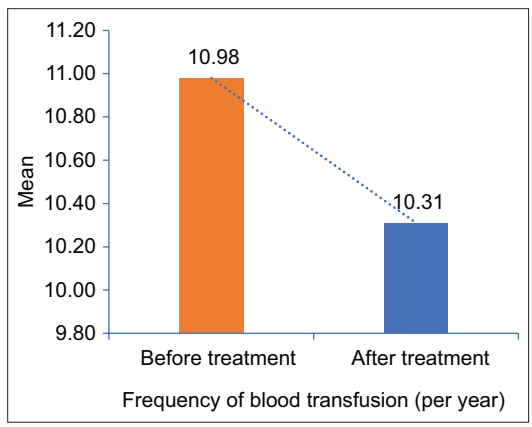

Figure 2: The mean frequency of blood transfusion before and after thalidomide treatment (n = 54)

aligns with the findings of Chen *et al.*[8] showed a significant increase in Hb 5.13 g/dL before treatment to 10.3 age g/dL after 3 months of treatment from a dose ranging from 50 mg/day to 200 mg/day. Nag *et al.*[9] showed over 1-year baseline Hb increased from 6.4 g/dL to 8.3 g/dL in complete responders (71.4%) and 23.9% were non-responders. Ali *et al.*,[10] where a significant enhancement in mean Hb levels was observed in the 6th month (1.4 g/dL increase) and 30th month (2 g/dL increase) though there was variability in thalidomide dosage 1.9 mg/kg/day in excellent responders, 2.1 mg/kg/day in good responders and 2.6 mg/kg/day among partial responder. Similarly,

Lu *et al.*[11] reported a mean increase of 1.5 g/dL in Hb levels following thalidomide therapy in eight studies of meta-analysis. This improvement in Hb levels and the potential cessation of transfusions could be attributed to the HbF-inducing properties of thalidomide, influencing α and β globin chain ratio and mitigating ineffective erythropoiesis. Moreover, Begum *et al.*[7] reported a significant increase in Hb levels from 7.04 ± 0.53 g/dL to 8.39 ± 1.44 g/dL after 31 months of thalidomide treatment. Kakkar *et al.*[12] showed that a low dose (1 mg/kg/day) of thalidomide was as efficacious as the standard dose (2 mg/kg/day) in reducing transfusion requirements. Jiskani and Menon[5] demonstrate a significant rise in mean Hb from 8.93 ± 1.04 g/dL to 10.54 ± 1.18 g/dL over 6 months of thalidomide treatment. These combined findings suggest a consistent trend of Hb improvement across various studies, both short-term and long-term periods, showing a significant rise of Hb, though dosage varies in different studies. The current study indicates a significant decrease in blood transfusion numbers from a mean number of 10.98 ± 1.41 before treatment per year to a mean of 10.31 ± 1.36 after 12 months of treatment. This aligns with findings from several studies, Yassin[4] reported a significant decrease in yearly transfusion from 27 to 7.79 blood units per year. Yang *et al.*[13] observed a similar response, where a significant drop in yearly transfusion from 20.7 to 5.8 blood units per year. Begum *et al.*[7] reported 35.3% of patients with no requirement for blood transfusion after treatment of thalidomide over 31 months. Chandra *et al.*[6] observed that 40.5% of patients became transfusion-free after treatment, and the mean baseline transfusion requirement was 75 mL/kg, which reduced significantly over 6 months' mean requirement of 38.9 mL/kg. Ali *et al.*[10] reported a similar result where they observed that 76.7% of patients are completely transfusion-independent over 35 months. Chen *et al.*[14] noted after 3 months of treatment with thalidomide, RBC transfusion volume significantly decreased to 5.4 ± 5.0 units, whereas the placebo group was 10.3 ± 6.4 units ($P < 0.001$). These collectively signify long-term studies can assess patients to become transfusion-free. Our study duration was only 1 year, so we could compare only the transfusion rate of pre- and post-treatment status, not transfusion-free interval.

Limitations of the study

The study had some limitations, including a relatively small sample size and a short follow-up period, which restricted the assessment of long-term effects and safety of thalidomide treatment in transfusion-dependent β-thalassemia patients. The absence of a control group further limited the ability to draw definitive conclusions regarding the efficacy of thalidomide compared to standard treatments or no treatment. In addition, the study did not comprehensively evaluate potential adverse effects and long-term safety considerations associated with thalidomide in this patient population. Moreover, being a single-center study, the findings may lack generalizability to a broader and more diverse patient population.

Conclusion

Exploration of the effects of thalidomide in transfusion-dependent beta thalassemic patients within the present study provides valuable insights into its therapeutic potential. The study demonstrated significant improvements in Hb levels and a noteworthy decrease in blood transfusion frequencies. These findings align with prior research, supporting the notion that thalidomide can effectively ameliorate anemia and potentially impact transfusion frequencies.

Recommendation

- Larger-scale studies: Larger-scale prospective studies to further investigate the effects of thalidomide treatment in transfusion-dependent β-thalassemia patients
- Long-term follow-up: Long-term follow-up studies to assess the sustained effects and safety profile of thalidomide treatment in this patient population
- Comparative studies: Comparative studies with control groups to compare the effects

of thalidomide treatment with standard treatments

- Multicenter studies: Multicenter studies involving diverse patient populations enhance the validity of the findings and account for potential variations in patient demographics and clinical characteristics
- Adverse effect monitoring: Systematic monitoring of adverse effects associated with thalidomide treatment in transfusion-dependent β-thalassemia patients to ensure patient safety and assess the risk-benefit profile of the treatment.

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Conflicts of Interest

None declared.

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