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Research Article

Comparison of Efficacy and Safety of Thalidomide *vs* Hydroxyurea in Thalassemia Patients: A Single-Centre Pilot Study

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Abstract: Background: Beta thalassemia is a genetic disorder causing defective beta globin chain formation, leading to ineffective erythropoiesis and hemolysis. It has three types: thalassemia major, thalassemia intermedia, and thalassemia minor. Treatment options include blood transfusions, iron chelation therapy, and bone marrow transplantation, but new treatments like HbF inducers (e.g., hydroxyurea) and erythropoiesis modulators are being developed. Thalidomide and hydroxyurea are also being used to manage thalassemia by increasing HbF synthesis and reducing transfusion frequency.

Objective: To compare the efficacy and safety of thalidomide and hydroxyurea in beta-thalassemia patients for a period of six months.

Materials and Methods: A Prospective interventional single-centre study was conducted the tertiary care hospital of southern Pakistan, from 1st September 2021 to 3rd March 2022. A total of 39 patients of beta thalassemia major and intermediate with age ranges of >10 and <30 years were enrolled in this study. 24 patients were fulfilling the study requirement. Thalidomide was started with a dose of 50 mg/day (in patients >10-13 years) while the adult dose was 100 mg /day (age >13 Years) every night. Hydroxyurea was given at 15 mg/kg /day. Pre and post-treatment tests were done. For assessing the safety of thalidomide and hydroxyurea biochemistry test was done along with LDH, Platelets counts, and WBCs count. The efficiency of both drugs was analyzed by hemoglobin, reticulocyte count, nucleated red blood cells, MCV, MCHC, white blood cells, and platelets.

Result: Both groups showed a highly significant increment in Hb. Thalidomide treated group baseline was 6.8 ±1.3 and after 06 months 8 ±13; (p-value <0.001). Furthermore, reticulocyte count was highly significantly augmented in HU treated group (p-value <0.001) Hydroxyurea-treated group showed significant decline in NRBC with a difference of -2.3±1.1 (p-value 0.02). Moreover, the transfusion interval was more significantly increased in the thalidomide group. The hemolysis parameter, LDH significantly declined in both groups. The hydroxyurea-treated group showed difference of -62.4±124.4 (p-value 0.03) while the thalidomide-treated group showed a difference of -64.36±32.9 (p-value 0.05). AST was only significantly decreased in thalidomide treated group.

Conclusion: Among both groups, hemoglobin, RBCs and reticulocyte count levels raise in both groups while NRBCs significantly decrease in HU treated group. Moreover, transfusion interval was also significantly increased by thalidomide. It shows safety by significantly decreasing the TBIL and AST, whereas LDH was decreased in the HU-treated group. This clinical trial was registered as # NCT06239389.

Keywords: Qualitative research, Pharmacovigilence, Genetics, Clinical pharmacology, Haematology, Anemia.

INTRODUCTION

Beta thalassemia is genetic disorder inherited as autosomal recessive pattern resulting from defect in formation of beta globin chain. On the basis of severity thalassemia is divided into three types that are thalassemia major, which is also known as Cooley's anemia; thalassemia intermedia; and thalassemia minor also referred as beta thalassemia trait or beta thalassemia carrier [1]. Due to unavailability of beta globin chain of hemoglobin free alpha globin take part in formation of reactive oxygen species and lead to ineffective erythropoiesis or hemolysis; secondary to the destruction of red blood cells in bone marrow [2].

An individual with thalassemia major needs medical attention in the first two years of life because they fail to thrive and turn out to be pale. Some of the clinical features are diarrhoea, recurrent fever, and progressive enlargement of abdomen, growth retardation, jaundice, skin pigmentation, craniofacial changes and osteoporosis [3].

Symptoms include pallor, jaundice, and hepatosplenomegaly swelling and growth retardation. Moreover, patients with milder symptoms appear with microcytic anemia without any complication and history of blood transfusions is diagnosed with thalassemia intermediate [2].

Thalassemia major (homozygous thalassemia) patients need frequent blood transfusions. If the patient does not maintain

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hemoglobin greater than 7.0gm/dl excess erythropoietin is released and leading skeletal deformities hepatosplenomegaly and increase in gastrointestinal iron absorption [4]. Repeated blood transfusion on the other hand leads to iron overload so iron chelation therapy also required for removal of excess iron acquired by blood transfusions [5].

As previously stated, bone marrow transplantation, blood transfusions, iron chelation therapy are the management options of thalassemia patients but because of high cost , un-identical donor of bone marrow transplant, unsafe blood transfusions and poor compliance with chelation therapy decrease the feasibility of these choices. So substitute treatment choices that help in gamma globin chain imbalance and effectively reduce the need of iron chelators are considered [6].

Many of HbF inducers were identified like azacitidine, decitabine, sodium butyrate and hydroxyurea. Among these, except hydroxyurea are under investigation and not use in clinical practice [7].

Erythropoiesis modulators like transforming growth factors – β and JAK-2 inhibitors are the drugs under development for these patients. Activins belongs to TGF- β work as a regulator of erythropoiesis and help in diverse cellular response. Signaling of TGF- β superfamily inhibited by modified activin II b receptor and aids the maturation of erythroblast differentiation. Studies suggest that JAK-2 inhibitor ruxolitinib mitigate the ineffective erythropoiesis and shrink the spleen [8]. According to phase 3 trail, Luspatercept mature erythroid cells, it shows the tendency to reduce the transfusion frequency in transfusion dependent beta thalassemia [9].

Thalidomide

Thalidomide lies under the classification of immunomodulatory agents. It has anti-angiogenic and anti-inflammatory effects. By facilitating the proliferation of erythroid cells, gamma globin gene expression and ultimately HbF synthesis [10].

Firstly it was introduced for the management of morning sickness in pregnancy, later on it was abandoned because of its teratogenic effects. Then many years later drug shows its effects towards multiple myeloma and leprosy [11]. In 2008, its use was reported very first time for thalassemia which were followed by many other case series and case report [12].

Hydroxyurea

An antineoplastic drug, hydroxyurea produces its effect by compensating the hallmark sign of beta thalassemia (i.e. disproportion of alpha and beta globin chains) by the induction of HbF synthesis. Hydroxyurea increases the gamma globin chain synthesis (that enhancing the HbF production) and play role in compensation of defaulted beta chain by the formation of gamma globin chain [13].

Hydroxyurea got the approval by food and drug administration as an HbF inducer [14]. As it is an antineoplastic drug so used in different myeloproliferative disorders [15]. Although it's exact mechanism of action is controversial; but, among different proposed mechanism of action most accepted mechanism is its cytotoxic action secondary to stress erythropoiesis due to augmentation of HbF it decreases the frequency of blood transfusion and iron chelation [16].

MATERIALS AND METHODS

The prospective interventional single centre study was conducted at the tertiary care hospital of southern Pakistan, from 1st September 2021 to 3rd March 2022. After taking an institutional ethical committee clearance, total of 39 patients of beta thalassemia major and intermediate with age range of >10 and <30 years were enrolled in this study, subsequent to taking prior informed consent from patients or their legal guardians as applicable. Patients on any other haemoglobin F inducer or erythropoietin also with co-morbidities like cardiopulmonary and neurological disease were excluded from study. Moreover, pregnant, lactating women and patient did not willing to take contraceptive measures were also not included; additionally participants with history of thrombosis were not fit for this study. A thorough history was taken with relevant clinical information to gather the basic demographics and clinical parameters. A baseline evaluation was routinely done to eliminate any renal and hepatic dysfunction, cytopenias, high ferritin and thrombocytopenia. After running baseline screening test for eligibility in 39 patients, 15 participants were eliminated due to viral hepatitis, high ferritin and history of cirrhosis. Remaining patients were divided into two groups. All female patients were counselled about teratogenic effect of thalidomide.

Thalidomide was started with the dose of 50 mg / day (in patients >10-13 years) while the adult dose was 100 mg /day (age >13 Years) every night. Aspirin (75mg/day) prescribed to patients for the prevention of thrombotic events. Hydroxyurea was given with 15 mg/kg /day. Patients were counsel about adverse effects. Iron chelators were continued as per standard guidelines.

For assessing the safety of thalidomide and hydroxyurea liver, and kidney function test were advised along with lactate dehydrogenase test before starting the drugs. Platelets counts and white blood cells checked and all tests were repeated at the interval of six months. Sample for aspartate aminotransferase, alanine aminotransferase, total bilirubin, indirect bilirubin, urea, creatinine and lactate dehydrogenase were taken in red top vacutainer containing no clot activators, anticoagulants, preservatives or separator material.

Efficiency of both drugs was analyzed by complete blood picture. Blood sample for accessing the haematological parameters were collected in vacutainer tubes (purple top which contain anticoagulant EDTA). Parameters include haemoglobin, reticulocyte count, nucleated red blood cells, MCV, MCHC, white blood cells, platelets check via sysmex XN-1000.

The threshold for transfusion was kept at Hb <7g/dl or as per patient's demanding clinical condition (infection and growth retardation). On the contrary, transfusion duration were recorded carefully.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

STATISTICAL ANALYSIS

The quantitative variables are shown in Mean ± Standard Deviation, and qualitative variables as ratio/frequency/percentage. Normality was checked by Shapiro Wilk Test. Independent sample t test or Man Whitney test was performed for evaluating differences within the group. Pre and post treatment was analyzed by Paired sample t test or Wilcoxin Sign Test. Chi-Square/ Fisher Exact test was applied for qualitative variables. P-value of <0.05 was assumed as significant.

RESULT

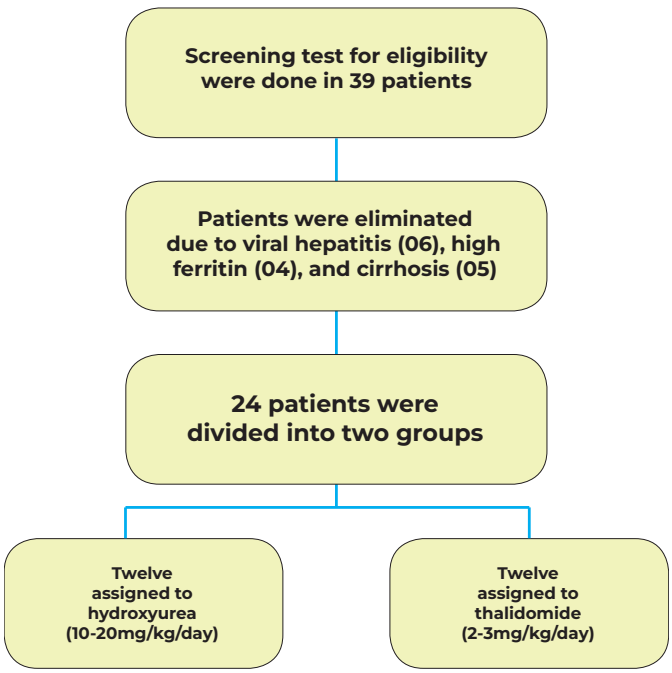


Fig. (1). Profile Shows Screening and Selection of Patients for Both Arms of Study.

A total of 24 patients were enrolling in study that was divided into 2 groups. In hydroxyurea group among the 12 patients half were female and remaining male, aged between 10-30 years (14.5 ±.60). Ferritin was 2144.25 ±1416.89. Ten patients were known case of beta thalassemia major other 02 were thalassemia intermediate. On another side in thalidomide group seven male and five female were enrolled age between 11.18 ± 2.13. In second group 91% patients were the known case of thalassemia major while average ferritin was 2539.08 ±10.23.5. Other details including onset of disease, Hb electrophoresis of both group are listed in Table **1**.

Table 1. Baseline Parameters of Thalidomide and Hydroxyurea Groups.

Characteristics	Group 1 (HU)	Group 2 (Thalidomide)	p-value
Sex (Male : Female)	6:6	7:5	0.33+
Age (years)	14.5 ± 5.60	11.18 ± 2.13	0.09*
Age at Diagnosis (M)	28 ± 20.19	11.75 ± 5.81	0.02*
Weight (kg)	32.16 ± 12.03	31.75 ± 8.103	0.922*
Beta- Thalassemia Type			
β- thalassemia Major	10 (83.33%)	11 (91.66%)	1+
β- thalassemia Intermediate	2 (16.66%)	1 (8.33%)	
Haemoglobin Electrophoresis at the Time of Diagnosis			
Haemoglobin F (%)	79.625 ± 29	78.95 ± 14.46	0.326*
Haemoglobin A (%)	10.81 ± 18.08	13.51 ±10.98	0.236+
Haemoglobin A_2 (%)	2.641 ± 1.66	3.29 ± 2.48	0.34*
Ferritin	2144.25 ± 1416.89	2539.08 ± 1023.5	0.422*

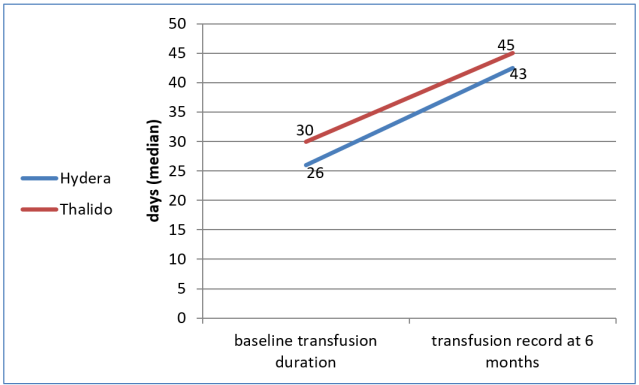
If not then Fisher exact test.
*Mann-Whitney test.
+Independent sample t test.
Total no. of patient/group (n) =12.
Interpretations mentioned as in Average ± SD (Standard deviation).
p- value calculated with paired independent sample t-test.
P-value of <0.05 was assumed as significant.

Analysis of Drug Efficacy Parameters

Both groups showed highly significant increment in Hb. Thalidomide treated group (baseline 6.8 ±1.3 and after 06 months 8 ±13; p-value <0.001) while hydroxyurea treated group also showed approximately identical results (baseline 6.2 ± 1.4 and after 06 months 8.0 ±1.4; p-value <0.001). RBC was also very significantly raised in thalidomide treated group that was 2.7 ±0.4 at baseline whereas at the end of study it increased to 3.3±0.5 (p-value <0.001), hydroxyurea arm also indicate very significant rise in RBC count (at 0 month 2.6 ±0.6 and at 6 months 3.4 ±1.0; p-value 0.01).

Red blood cells indices including MCV, MCH, and MCHC didn't show any significant changes in both groups. Furthermore, reticulocyte count was highly significantly augment in HU treated group (baseline 2.1±1.1 and post treatment 3.4 ±1.2;

p-value <0.001) whereas in thalidomide treated group it also showed very significant improvement that was 1.2 ±0.9 p-value 0.02 (calculated by wilcoxon Sign Test) as shown in Fig. (**1**). Hydroxyurea treated group showed significantly decrease in NRBC with the difference of -2.3±1.1 (p-value 0.02).



Total No. of patient/group (n) =12.
Interpretations mentioned as in median (IQR).
P-value of <0.05 was assumed as significant.

Fig. (2). Comparison of Transfusion Interval between Both Groups.

Furthermore, transfusion frequency was significantly decreased in both groups but thalidomide has significantly greatest effect on transfusion interval than hydroxyurea as shown in Fig. (**2**).

Analysis of Parameters Predicting Hemolysis

Total bilirubin was showed very considerable decrease in thalidomide treated group respectively. Total bilirubin decrease -0.9 ±0.2 (p-value 0.001).While in second group no significant difference were noticed. Another parameter reflecting hemolysis including LDH, which was significantly declined in both groups. Hydroxyurea treated group showed LDH difference of -62.4±124.4 (p-value 0.03) while thalidomide treated group showed difference of -64.36±32.9 (p-value 0.05) as shown in Table **2**.

Analysis of Safety Parameters

AST was only significantly decreased in thalidomide treated group. Moreover, ALT didn't give any significant results. Urea and Creatinine didn't reveal as the significant parameters in both hydroxyurea and thalidomide treated groups as shown in Fig. (**2**). Moreover, WBCs was only significantly augment in thalidomide group (p-value 0.01 calculated by Wilcoxon sign test). Platelets have no significant effect in both groups.

Table 2. Comparison of Haemoglobin, RBCs Indices, WBCs, PLTs, LDH, Liver and Kidney Function Test between Hydroxyurea and Thalidomide Treated Groups.

	Treatment group									
	Thalido					**Hydera**				
	Pre-treatment	**Post treatment**	**d**	**t**	**P-value**	**Pre-treatment**	**Post treatment**	**d**	**t**	**P-value**
Hb	6.8 ±1.3	8 ±1.3	1.3 ± 0.5	2.4	<0.001	6.2 ± 1.4	8.0 ± 1.4	1.8 ± 0.6	3.2	<0.001
RBC	2.7 ±0.4	3.3 ± 0.5	0.6 ± 0.2	3	<0.001	2.6 ± 0.6	3.4 ± 1.0	0.8 ± 0.3	2.3	0.01
MCV	75.1 ± 8.7	73.2 ± 17.6	-1.9 ± 5.7	-0.33	0.71	76.2 ± 8.2	73.3 ± 7.0	-3.0 ± 3.1	-0.9	0.36
MCH	25.2 ± 3	26.2 ± 4	1 ± 1.4	-0.7	0.38	25.2 ± 3.0	24.4 ± 3.4	-0.8 ± 1.3	-0.6	0.55
MCHC	34 ± 1.3	33.2 ± 2.2	-0.8 ± 0.7	-1.1	0.2	33.1 ± 2.5	32.3 ± 4.0	-0.8 ± 1.4	-0.6	0.47
RET	2.6 ± 2.4	3.8 ± 2.2	1.2 ± 0.9	1.3	0.02+	2.1 ± 1.1	3.4 ± 1.2	1.3 ± 0.5	2.9	<0.001
NRBC	1.3 ± 3.3	1.6 ± 3.3	0.2 ± 1.3	0.2	0.4+	2.9 ± 3.9	0.6 ± 0.9	-2.3 ± 1.1	-2.0	0.02+
LDH	290.9 ± 98.1	226.7 ± 58	-64.3 ± 32.9	-1.9	0.05	410.4 ± 341.3	348 ± 263.2	-62.4 ± 124.4	-0.5	0.03+
TBIL	1.5 ± 0.6	0.6 ± 0.2	-0.9 ± 0.2	-5.3	0.001	1.9 ± 1.6	1.8 ± 1.2	-0.1 ± 0.6	-0.1	0.78+
IBIL	0.8 ± 0.29	1.4 ± 0.4	0.6 ± 0.1	4	0.006	1.1 ± 1.1	1.2 ± 1.3	-0.1 ± 0.5	-0.2	0.62+
Cr	0.4 ± 0.1	0.5 ± 0.5	0.1 ± 0.1	1	0.9+	0.5 ± 0.3	0.4 ± 0.1	-0.1 ± 0.1	-0.7	0.49
UREA	27.1 ± 7.8	25 ± 10.7	-2.1 ± 3.8	-0.5	0.343	22.6 ± 7.2	24.7 ± 9.2	2.1 ± 3.4	0.6	0.56
SGOT AST	145.7 ± 14.6	58.6 ± 28	-87.1 ± 9.1	-9.6	0.03+	48.3 ± 15.2	39.1 ± 10.7	-9.2 ± 5.4	-1.7	0.09
SGPT ALT	79.5 ± 50	74.6 ± 39.7	-4.9 ± 18.5	-0.3	0.714	39.4 ± 20.0	34.8 ± 16.6	-4.6 ± 7.5	-0.6	0.97+
WBC	7.34 ± 2.9	10.2 ± 6	-2.9 ± 1.9	1.5	0.01+	7.1 ± 3.3	7.1 ± 2.6	-0.0 ± 1.2	-0.0	0.98
PLTs	339.3 ± 207.4	291.4 ± 102	47.8 ± 66.7	-0.7	0.298	313.3 ± 130.7	256.3 ± 82.8	-56.9 ± 44.7	-1.3	0.08

If not then Paired Independent sample t- test.
+Wilcoxon Sign Test.

DISCUSSION

Only curative option for the treatment of BTM is hematopoietic stem cell transplant but because of its cost majority of patients doesn't afford it [17]. Meanwhile, role of HbF inducers are more prominently emerge in the treatment of beta thalassemia since the few decades. Fetal haemoglobin contain γ globin gene it decrease the imbalance between alpha and non-alpha chains so decreasing the worsening outcome of β thalassemia [4]. Depending upon mechanism of action HbF inducers are divide into categories named as cytotoxic agents, short chain fatty acids, immunomodulatory drugs, chemotherapeutic drugs, mTOR inhibitor and DNA binding agents [13].

In this study we evaluate and compare the safety and efficacy of two HbF inducers one belongs to chemotherapeutic drug although other lie in the category of immunomodulatory agents named as hydroxyurea and thalidomide respectively.

Both drugs shows advantageous effect in transfusion dependent and non-transfusion dependent beta thalassemia patients so our motive to compare the both drugs via various parameters.

Next to screening for eligibility patients were separated into two groups each have twelve patients. Safety profile was analyzed by checking the liver and kidney function analysis, lactate dehydrogenase, WBCs and platelets; while efficacies were test by haemoglobin, RBC and its indices, transfusion frequency, reticulocytes count and NRBCs.

Both drugs shows similar raised hemoglobin that are statistically very significant because both drug belong to HbF inducer and have potency to escalate the level of hemoglobin in the period of 6 months, in the approximation of earlier studies [18].

Under test drugs also represent the increase in red blood cells, hydroxyurea treated group comparatively shows lower upturn than thalidomide group that must be highly significant. Thalidomide as a HbF inducer must possess the greater activity in thalassemia patients than hydroxyurea. *In vitro* studies suggest that enhancement of HbF levels may also be possibly achieved by elevation in ROS levels that launch the P38 MAPK pathway [6]. Moreover, in comparison of three RBCs indices (MCV, MCH, MCHC) Hydroxyurea and thalidomide tested groups shows not significantly alteration in levels that reflect its relation with these parameters [19].

As a HbF inducer , main action of both drugs are changing the ineffective erythropoiesis to the effective erythropoiesis one in term of increasing the reticulocyte count and decreasing the nucleated red blood cells, hydroxyurea groups shows the highly significant raise reticulocyte count whereas thalidomide also show upturn in reticulocyte count that is very significantly in this study whereas another mean to compare the efficacy of both groups we compared the NRBCs at the six months of interval after giving the drugs to respective groups and we analyze hydroxyurea have greater effect and resolve the ineffective erythropoiesis significantly in comparison thalidomide group have not significant alternation in nucleated red blood cells that is not consistent with previous studies [20].

Another important part of study is efficacy comparison of HbF inducers (hydroxyurea and thalidomide) in term of other variables. After treatment with hydroxyurea and thalidomide total bilirubin were very significantly decrease in thalidomide group whereas hydroxyurea group doesn't show any significant elevation in total bilirubin , also when compare the another parameter for liver function analysis that is indirect bilirubin, it significantly increase in thalidomide group (that may be by increased in red blood cell turnover) and again no alternation was observed in other group that visualize understudy immunosuppressant have more beneficial effect on liver and decrease the hemolysis of RBCs, furthermore, another parameter for checking the same effect is lactate dehydrogenase, on analysis decrease in under study anti chemotherapeutic drug that also consider as significant in term of p-value. So both drugs have positive effects in prevention of hemolysis of RBCs [20].

Liver enzymes such as AST significantly decrease in thalidomide treated group while it is not show any significant alternation in hydroxyurea treated group another under study enzymes to check the liver status is ALT which show insignificant alternation in both under tested groups that clearly indicate less chance of liver damage were consider in thalidomide group, as previously mentioned Aspartate aminotransferase is the indicator of liver damage or injury also it indicate the injury of other organs like kidney and heart [21].

On analysis, Patients on thalidomide and hydroxyurea confirm statistically insignificant alternation in kidney function analysis that is Creatinine and urea. Increase urea levels are indicative of speedily erythrocyte turnover [17]. Furthermore, variation in pre-treated and post treated Creatinine levels are secondary to the complication of beta thalassemia that include severe anemia, iron overload and low oxygen in tissue. Hypoxia is another symptom of anaemia that compensate with both HbF inducers and iron overload may be prevented by implication of conventional management of beta thalassemia that are effective iron chelators so it results in non-significantly alternation in both groups and are gain represent the efficacy of both drugs [22].

Upon comparison thalidomide and hydroxyurea groups platelets are insignificantly alter, in previous studies thalidomide have increase the risk of thrombosis which was not reported in this study that means patients did not complain about deep vein thrombosis, majorly reported ADR by thalidomide which reflects the safety of thalidomide. Another blood cell test in this study was white blood cells which was significantly raise in thalidomide treated group, this finding is notably different from the finding reported by Zahid *et al*.[23]. Moreover, opposite drug doesn't show any statistically significant alternation [13].

Blood transfusion requirement was more prominently decrease in thalidomide treated group, that consistent with the findings from other studies [24, 25], suggesting thalidomide as a good HbF inducer. Alternatively, patients on hydroxyurea also trans-

fused blood lately but in comparison, thalidomide have high efficacy towards maintaining the Hb and behave as better haemoglobin F inducer in beta thalassemia patients.

CONCLUSION

Considering the fact that, HbF inducers have greatest part in downgrading the clinical complications of beta thalassemia. This prospective study was conducted to assess the efficacy and safety of HbF inducers which proclaim that both represent the good effect on haemoglobin induction whereas RBCs increment was more prominently seen in thalidomide group. Moreover, ineffective erythropoiesis was effectively reduced by both groups but comparatively hydroxyurea have slightly higher effect than another understudy drug. Additionally, in terms of safety thalidomide showed better profile evaluated by lactate dehydrogenase, liver and kidney function test, than hydroxyurea. Lastly, another parameter of study transfusion interval was significantly increases among thalidomide treated patients. That shows the efficacy of understudy immunosuppressant as the superior HbF inducer. Along with efficacy, safety must be kept in view during therapy, which was exceptionally manifested by thalidomide group. Taking this into account, larger trials of hydroxyurea and thalidomide should be set to check the long term effects of drugs.

AUTHORS' CONTRIBUTION

The authors confirms contribution to the paper as follows:

- **Safia Mehmood Khan**: Conceptualization, Format analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing- original draft, Review and Editing.
- **Nuzhat Sultana**: Format analysis, Supervision.
- **Saima Siddiqui**: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing, Review and Editing.
- **Muhammad Nizammudin**: Data curation, Methodology.

DECLARATIONS

Data Sharing Statement

The clinical trial data of this article will not be shared.

Ethics Approval and Consent to Participate

This study involves human participants and was approved by institutional review board/ Ethic committee NIBD & BMT with protocol approval #: NIBD/IRB-236/21-2021.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

CONFLICT OF INTEREST

This manuscript has been extracted from M. Phil thesis work of Safia Mehmood Khan.

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