

# Mahidol Scoring for Assessing Various Grades of $\beta$ Thalassemia Intermedia

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## ABSTRACT

**Objective:** To determine the effectiveness of Mahidol Scoring for assessing various grades of  $\beta$  thalassemia intermedia.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Fatima Memorial Hospital, Shadman, Lahore, from August 2016 to August 2017.

**Methodology:** A total of 150 patients, both inpatient and outpatient diagnosed as thalassaemia intermedia fulfilling inclusion criteria, were enrolled, interviewed and examined after an informed consent. All patients were assessed by using Mahidol Scoring system. Their scores were documented on a predesigned evaluation performa. Patients were labelled as mild, moderate or severe diseased.

**Results:** In a total of 150 patients, 88 (58.7%) were males and 62 (41.3%) were females. Using Mahidol Scoring, 88 (58.7%) were labelled as mild, 53 (35.3%) as moderate and 9 (6%) as severe diseased. Patient who were labelled as mild diseased according to Mahidol Scoring, had no blood transfusions and showed good response to hydroxyurea. Patients with moderate score, were infrequently transfused and showed variable response to hydroxyurea. Patients in severe group received first transfusion at an early age, maintained lower Hb levels, showed growth retardation, splenomegaly, and had poor response to hydroxyurea.

**Conclusion:** Mahidol Scoring system is an easy, safe and effective way for classification of thalassaemia Intermedia severity. The grades according to Mahidol Scoring system will aid in the management of patients as the score can be quickly calculated, and can assist the clinician in an initial evaluation for disease severity in patients of thalassaemia intermedia.

**Key Words:** *Thalassemia intermedia, Mahidol scoring, Non-transfusion-dependent thalassemia.*

## INTRODUCTION

In  $\beta$ -thalassemia, there is either a complete absence of  $\beta$ -globin chain production ( $\beta^0$ -thalassemia) or a partial reduction ( $\beta^+$ -thalassemia). Thalassemia minor is heterozygous state and major is homozygous state. Intermedia can be either homozygous or heterozygous and there is substantial clinical overlap between these conditions.<sup>1</sup>  $\beta$  thalassemia intermedia patients can be completely asymptomatic until first or second decade of life, experiencing only mild anemia, minimal splenomegaly without transfusion or requiring occasional blood transfusions during acute infections, stress or blood loss. These patients come under the umbrella of non-transfusion-dependent thalassemsias (NTDT).

NTDT is a term used to label patients who do not require regular transfusions for survival, although they may

require occasional or even frequent transfusions in certain clinical settings and for defined periods of time.<sup>2</sup> NTDT encompasses three clinically distinct forms:  $\beta$ -thalassemia intermedia, mild/moderate/hemoglobin E/ $\beta$ -thalassemia, and  $\alpha$ -thalassemia intermedia (hemoglobin H disease).<sup>3</sup>

Hemoglobin E/ $\beta$ -thalassemia currently affects around 1,000,000 people worldwide.<sup>4</sup> It is the commonest haemoglobinopathy in Thailand, India, Laos and Cambodia, where carrier frequencies may reach as high as 80%.<sup>5</sup>

Mahidol University devised a scoring system to assess severity of Thal/E disease and named it Mahidol Scoring. This scoring system is based on different parameters which include steady state hemoglobin level, age at disease presentation, age of receiving first blood transfusion, requirement for transfusion, splenic size, growth and development (Table I). The total sum of all scores is then interpreted as follows: mild hemoglobin E/ $\beta$ -thalassemia (severity score <4); moderate hemoglobin E/ $\beta$ -thalassemia (severity score 4-7); and severe hemoglobin E/ $\beta$ -thalassemia (severity score >7).<sup>6</sup>

$\beta$ -thalassemia is the commonest inherited hematological disorder in Pakistan. It is estimated that around 60-80 million people in the world carry the thalassemia trait.<sup>7</sup> Prevalence of thalassemia carriers in Pakistan is 5-8%; but in targeted family, the carrier rate is 34%.<sup>7</sup> This high carrier rate has resulted in substantial number of thalassemia intermedia patients which escape correct

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Received: September 24, 2018; Revised: February 01, 2019;

Accepted: March 07, 2019

diagnosis and management. These patients present late without transfusion and often have raised HbF up to 99%.

This study was conducted to evaluate the effectiveness of Mahidol Scoring for assessing various grades of  $\beta$  thalassemia intermedia in Pakistani population, which will help to decide a suitable management plan.

### METHODOLOGY

This study was conducted in Department of Pediatric, Fatima Memorial Hospital, Shadman, Lahore from August 2016 to August 2017. Data collection was started after approval from Ethical Review Board. A total of 150 patients, diagnosed as Thalassaemia intermedia fulfilling inclusion criteria, were enrolled, interviewed and examined after an informed consent. These patients were diagnosed thalassaemia intermedia according to international guidelines, prior to start of study were taking either hydroxyurea or blood transfusion and were on regular follow-up in Fatima Memorial Pediatric Department. Patients with established cardiomyopathy and endocrinopathies like diabetes mellitus, hypoparathyroidism, and hypothyroidism were excluded from the study. All patients were assessed using Mahidol Scoring system and information include: Hb electrophoresis result at the time of diagnosis, response to hydroxyurea, blood transfusion require-ment, change in blood transfusion frequency after start of hydroxyurea and their scores were documented on a predesigned evaluation proforma. Patients were followed 3- and 6-monthly (Table I).

Response to hydroxyurea was divided into three categories.<sup>7</sup> Good response was considered as tranfusion independence with final hemoglobin (Hb) >8.0 g/dl in tranfusion dependent patient and a rise in hemoglobin  $\geq 2$  g/dl in tranfusion independent patient. Partial response was tranfusion independence with rise in Hb >2 g/dl but final Hb of <8 g/dl or reduction in tranfusion frequency by 50% in tranfusion dependent

patients and rise in Hb between 1-2 g/dl in tranfusion patients. No response was no rise of Hb in tranfusion independent or same level of tranfusion dependency in tranfusion dependent patients.

Data was entered and analysed in SPSS version 23. Descriptive statistics were performed on all the variables. All categorical variables were presented in the form of frequencies and percentages. Bar charts were constructed for categorical variables. Quantitative variables were presented in the form of mean  $\pm$  standard deviation. Chi-square test was used to see statistical significant association between the variables. P-value <0.05 was considered significant.

### RESULTS

Out of 150 patients, 88 (58.7%) were males and 62 (41.3%) were females. Using Mahidol Scoring, 88 (58.7%) were labelled as mild, 53 (35.3%) as moderate and 9 (6%) as severe disease. Consanguinity was present in 131 (87%) children in the study group.

Among 150 patients, there were 76 (50.7%) children who were diagnosed as cases of thalassemia intermedia in their early childhood between 1 - 5 years. It was followed by 44 (29.3%) children in their infancy, and 19 (12.6%) were diagnosed between age of 6-10 years. However, 11 (7.3%) were diagnosed at age >10 years.

There were 74 (49.3%) children who were transfused for first time in their life at age between 1 - 5 years, followed by 46 (30.7%) at age <1 year, 10 (6.7%) patients between age 6-7 years and 5 (3.3%) patients transfused after 10 years of age. However, 15 (10%) were never transfused at the time of registration.

Normal growth pattern was seen in 68 (45%) patient, slight growth retardation seen in 36 (24%) patients and growth retardation seen in 46 (30.7%) patients. Spleen size less than 4 cm (Mahidol Score 0) in 61 (40.7%) patients, between 4-10 cm (Mahidol score 1) in 63 (42%) patients and greater than 10 cm (Mahidol score 2) in 26 (17.3%) patients.

Among mild group, 16 (10.7%) patients were never transfused, 20 (13.3%) had rare/seldom transfusion, 31 (20.7%) patients were occasionally transfused and 11 (7.3%) were frequently transfused. In moderate group 2 (1.3%) patients were never transfused, 8 (5.3%) patients needed rare transfusion, 19 (12.7%) needed occasional transfusion, 22 (14.7%) patients were frequently transfused. Only 1 (0.7%) patient was occasionally transfused while 8 (5.3%) children with severe scoring were frequently transfused. Overall, 34% (n=51) children were transfused occasionally (p <0.001), (Table II).

According to this study, 53 (35.3%) children of mild score followed normal growth pattern. In moderate group, 15 (10%) children were following normal growth centiles, 20 (13%) were slightly impaired and 18 (12%) were significantly impaired in growth. Whereas, in severe

**Table I:** Mahidol scoring system.

Steady-state hemoglobin (g/dl)			
Value	>7	6-7	<6
Score	0	1	2
Age of onset (years)			
Value	>10	2-10	<2
Score	0	0.5	1
Age at 1st blood transfusion (years)			
Value	>10	4-10	<4
Score	0	1	2
Requirement for transfusion			
Value	None/rare	Occasionally	Regularly
Score	0	1	2
Size of spleen (cm)			
Value	<4	4-10	>10
Score	0	1	2
Growth retardation			
Value	-	+/-	+,s/p
Score	0	0.5	1

**Table II:** Distribution of  $\beta$ -thalassemia intermedia in the studied group.

Categories	Mild	Moderate	Severe	P-value
Requirement of BT	n (%)	n (%)	n (%)	0.0001
Rare	20 (13.3%)	8 (5.3%)	0 (0%)	
Occasional	31 (20.7%)	19 (12.7%)	1 (0.7%)	
Frequently	11 (7.3%)	22 (14.7%)	8 (5.3%)	
None	16 (10.7%)	2 (1.3%)	0 (0%)	
Once	10 (6.7%)	2 (1.3%)	0 (0%)	
Change blood requirement				0.0001
0-20%	8 (5.3%)	15 (10%)	7 (4.7%)	
21-40%	22 (14.7%)	11 (7.3%)	2 (1.3%)	
41-60%	41 (27.3%)	24 (16%)	0 (0%)	
61-80%	17 (11.3%)	2 (1.3%)	0 (0%)	
>80%	0 (0.0%)	1 (0.7%)	0 (0%)	
Growth				0.0001
Growth retardation (+)	11(7.3%)	18(12%)	8(5.3%)	
No growth retardation (-)	53(35.3%)	15(10%)	0(0%)	
Slight growth retardation (+/-)	24(16%)	20(13.3%)	1(0.7%)	
Response to hydroxyurea				0.0001
GR (good response)	62 (41%)	23 (15.3%)	0 (0%)	
NR (no response)	3 (2%)	12 (8%)	6 (4%)	
PR (partial response)	23 (15.3%)	18 (12%)	3 (2%)	
SSHb				0.036
>7	61 (40.7%)	25 (16.7%)	4 (2.7%)	
6-7	25 (16.7%)	28 (18.7%)	5 (3.3%)	
<6	2 (1.3%)	0 (0%)	0 (0%)	
Spleen size				0.004
0 (<4 cm)	44 (29.3%)	16 (10.7%)	1 (0.7%)	
1 (4-6 cm)	26 (17.3%)	30 (20.0%)	7 (4.7%)	
2 (>6 cm)	18 (12.0%)	7 (4.7%)	1 (0.7%)	
Fetal hemoglobin				0.502
Less than 20%	5 (3.3%)	1 (0.7%)	0 (0%)	
20-50%	7 (4.7%)	6 (4%)	1 (0.7%)	
51-70%	14 (9.3%)	12 (8%)	2 (1.3%)	
71-90%	19 (12.7%)	17 (11.3%)	3 (2%)	
Greater than 90%	43 (28.7%)	17 (11.3%)	3 (2%)	

group, none followed normal growth pattern ( $p < 0.001$ ).

Following Mahidol Scoring, in mild group, 62 (41.3%) children showed good response to hydroxyurea and 23 (15.3%) were partial responders. In moderate group, 23 (15.3%) were good responders and 18 (12%) showed partial response. In severe group, 6 (4%) showed no response, while 3 (2%) showed partial response ( $p < 0.001$ ).

Following Mahidol Scoring, the documented reduction in need of blood transfusion by 41-60% seen in 41 (27.3%) children in mild group, 24 (16%) in moderate group and no reduction in severe group. Similarly, 61-80% blood transfusion reduction seen in 19 (12.7%) children and among them, 17 patients were from mild group ( $p < 0.001$ ).

Steady state hemoglobin greater than 7 g/dl was seen in total 90 (60%) patients. Out of them, 61 (40.6%) were in mild group, 25 (16.6%) in moderate group ( $p < 0.036$ ). Fetal hemoglobin greater than 90% was seen in 60 (42%) patients, among them, 43 (28.7%) were in mild group ( $p 0.502$ ).

## DISCUSSION

Thalassemia is an inherited disorder with autosomal recessive mode of inheritance.<sup>8</sup> According to the study conducted by Roy in India, male patients were 1.6 times as compared to females.<sup>9</sup> In this study, male predominance is prominent as there were 88 (58.7%) males as compared to 62 (41.3%) females; males were 1.4 times more as compared to females. This is because males tend to receive more care and treatment in local culture.

Mondal has described in his study that high incidence of thalassemia is because of endogamous norms of marriages.<sup>10</sup> A study conducted by Rehman and Ishaq documented 68% carrier rate in their studies for carrier detection in families with beta thalassemia.<sup>11,12</sup> Similarly, in this study, 87% ( $n=131$ ) children belonged to consanguinous. This has also been established that in a target family, carrier rate is 34% as compared to 5-8% in general population.<sup>7</sup>

In a study by Kaddah, 51.7% children were never transfused.<sup>13,14</sup> In the present study, only 10.7% ( $n=16$ ) were never transfused, one transfusion was given in less than one year in 30.7% and in 49.3% ( $n=74$ ) between 1 - 5 years.

In a study conducted by Shah, once or twice monthly blood transfusions are required in patients from 6-10 years of life (50%), while children >10 years are required 3-4 times transfusion per month.<sup>15</sup> In this study, children among mild group, frequent transfusions were required by only 11 (7.3%) children. While, 8 (5.3%) children with severe scoring were frequently given blood transfusion. Overall, 34% ( $n=51$ ) children in this study were transfused occasionally.

Growth retardation is characteristically seen in patients with thalassemia intermedia and is attributed to anemia and high ferritin levels.<sup>16</sup> According to Hashemi, short stature has been reported in 65.71% children suffering from thalassemia intermedia.<sup>17</sup> However, in this study, the trend was different as 53 (35.3%) children of mild variety followed normal growth pattern. In moderate group, only 15 (10%) children were following normal growth centiles, 17 (11%) were mildly impaired and only 1(0.6%) was severally impaired.

In a study conducted by Asif, 23% children showed good response to hydroxyurea, 72% partial response and only 5% no response.<sup>18</sup> In this study, in mild group, 62 (41.3%) children showed good response and only 23 (15.3%) were partial responders. In moderate group, 15.3% ( $n=23$ ) were good responders and 8% showed no response. In severe group, 4% showed no response while 2% showed partial response.

Blood transfusions are required by patients suffering from thalassemia intermedia in order to maintain steady state hemoglobin of ~ 10gm/dl. Bradai has documented that there is 50% reduction in need of blood transfusion

following hydroxyurea.<sup>19</sup> This advantage of using less transfusions and its related complications by treating thalassemia intermedia as NTDT are huge. In this study, by using Mahidol Scoring, the documented reduction in need of blood transfusion was 41-60% in 41 (27.3%) children of mild, 24 (16%) children in moderate and no reduction severe groups. Similarly, 61-80% reduction in 19 (12.7%) children and 89.4% among these were from mild group.

In this study, steady state hemoglobin  $\geq 6$  g/dl was seen in 148 (81.3%) children; 40.7% of these were from mild group. In another studies, Hydroxyurea is believed to increase hemoglobin concentration and; hence, reduces the need of transfusion.<sup>20,21</sup>

Splenomegaly is a characteristic finding in thalassemia intermedia due to hemolysis,<sup>22</sup> and extra medullary hematopoiesis. A total of 40 patients (70.2%) were reported to have splenomegaly in the study by Kaddah.<sup>14</sup> In this study, 59.3% children had variable size of spleen. However, spleen size  $< 4$  cm noticed in 44 (29.3%), 16 (10.7%) and 1 (.7%) in mild, moderate and sever groups, respectively.

## CONCLUSION

Mahidol Scoring system is an easy, safe and effective way for classification of thalassaemia intermedia severity. The grades, according to Mahidol Scoring system, will aid in the management of patients as the score can be quickly calculated, and can assist the clinician in an initial evaluation for disease severity in patients of thalassemia intermedia.

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