Correlation Between Mean Red Cell Transfusion Demand And Chelation Therapy In Multiply Transfused Thalassemia Major Patients

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Abstracts: Background & Objective: Life long red blood transfusion remains the main treatment for β thalassemia major patients. Transfusion-dependent patients, in the absence of chelation therapy, develop progressive accumulation of iron, which is responsible for tissue damage and, eventually, death. The factors, which influence the iron burden are type of chelation therapy and mean red cell transfusion requirement. Increasing red cell transfusion requirement, iron deposit and development of all antibodies complicates transfusion therapy in thalassemia patients. Aim is to investigate the patients for the red cell transfusion requirement compared on the basis of iron overload and type of chelation therapy. Methodology: Ninety eights patients were included in this study and samples collected and investigated for the red cell transfusion requirement, compared on the basis of iron overload and type of chelation therapy.Conclusion: Combination of two iron chelators (such as parenteral desferroxamine plus oral deferiprone) have been shown to produce additive and synergistic effects, may produce enhanced iron excretion, minimize side effects, decrease mean red cell transfusion requirement and improve compliance is strongly recommended in transfusion dependent thalassemia patients.[Jain R NJIRM 2015; 6(4): 54-57]

Key Words: Red Cell, Chelation Therapy, Thalassemia

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Introduction: Lifelong red blood transfusion remains the main treatment for β thalassemia major patients. Transfusion-dependent patients, in the absence of chelation therapy, develop progressive accumulation of iron, which is responsible for tissue damage and, eventually, death[1,2,3]. The factors, which influence the iron burden are type of chelation therapy and mean red cell transfusion requirement. Increasing red cell transfusion requirement, iron deposit and development of alloantibodies complicates transfusion therapy in thalassemia patients[1, 2, 3, 4].

Material and Methods: A retrospective study was conducted from February 2012 to December 2013. Ninety eights patients were included in this study and samples collected and investigated for the red cell transfusion requirement, compared on the basis of iron overload and type of chelation therapy. Iron overload in thalassemia patients was measured by serum ferritin levels.

Review of Literature: The most important long-term problem associated with regular transfusions in thalassaemia is iron overload. Blood contains iron which cannot be excreted from the body, and a typical thalassaemia patient on a regular transfusion will accumulate 0.3- 0.5mg/kg of iron per day. Excessive iron is toxic, the most vulnerable organs being the heart, liver and endocrine glands. Once the body has accumulated 12-24g of iron significant clinical manifestations of iron toxicity can be expected[5]**.** Without treatment to remove the iron, the majority of patients develop cardiac problems and die of heart failure by age of 20 [6-7].

Therapy to remove or 'chelate' excess iron is therefore essential and this must be started within a year of so of starting regular transfusions. The established regime requires subcutaneous infusions of the chelating agent desferrioxamine given 5-7 nights per week over 8-12 hours. This regime can stabilize the body iron load at an acceptable level in a majority of patients, and has been shown to reduce the risk of cardiac disease, and to improve survival[5, 6, 7, 8].

Deferiprone (L1) is a safe oral iron-chelating agent that decreases iron overload without causing considerable side-effects, and is safe if used under strict supervision, in transfusion-dependent iron overloaded children. Most studies found that the toxic side effects of the use of L1 were agranulocytosis (0.6%), musculoskeletal and joint pains (15%), gastrointestinal complaints (6%) and zinc deficiency (1%). However, the incidences of these toxic side effects are currently considered reversible, controllable and manageable, by using

lower doses of L1 or combination therapy with Desferrioxamine. It was also found that the combination therapy could benefit patients experiencing toxicity with Desferrioxamine, and those not responding to either chelator alone (9, 10). It has been found that oral doses of 50-120 mg/kg/day, or dose of > 75mg/kg/day in three equally divided doses is more effective than lower doses[10]. L1 was able to bring patients to a negative iron balance at a dose of 50-120 mg/kg/day, by increasing urinary iron excretion, decreasing serum ferritin levels and reducing liver iron in the majority of chronically transfused iron-loaded patients[9]. Another study showed that HCV-negative patients exhibited a significant decrease in serum ferritin after 6 and 12 months of Deferiprone therapy[10]. It was found that in patients inadequately chelated by daily dose of Deferiprone of 75 mg/kg body weight, increasing the dose of Deferiprone, or combining subcutaneous Desferrioxamine with Deferiprone therapy improves the efficacy chelation.

Results: In present study mean red cell transfusion requirement was 206.20 ml/kg/year (S.D. = 28.62). Majority of the children in this study i.e. 40 (41.67%) were undergoing hypertransfusion therapy and transfused red cells were in the range of 208-248 ml/kg annually. It was observed that the requirement of red cells transfusion increases with age of the patients. Out of 96 patients, 86 (89.58%) thalassemic children were on chelation therapy. Maximum numbers of patients 37 (38.54%) were on oral chelation therapy after this 35 (36.45%) patients on combined chelation therapy (Desferroxamine & oral chelation).

Only 14 (14.58%) were on parenteral (desferroxamine) chelation therapy. Out of 96 patients, 10 (10.41%) patients were not taking any chelation therapy. In present study the difference of mean red cell transfusion requirement among the all chelation therapy groups when compared with each other were found highly significant ($p<0.01$). The mean red cell transfusion requirement were minimum in combination therapy group (combination of two iron chelators such as parenteral desferroxamine plus oral deferiprone) followed by parenteral desferroxamine chelation therapy group, oral chelation therapy group and maximum in patients those started chelation therapy but discontinued.

A total of 98 patients were included in the study. Irregular red cell alloantibodies were found in 8 patients (8.16%) (Matrix Gel System, Tulip). Mean age of patients who developed red cell alloantibody was 11.36 years. Five patients developed single antibodies (3 patient anti-K, 1 patient Kp^a and 1 patient anti-C), while other three patients developed multiple antibodies (anti-D and anti-E, anti-D and anti-C, anti-E and anti-K).

Discussion: Annual red cell transfusion: The annual red cell transfusion is shown in table no. 2. Average yearly transfusion was 206.20 ml/kg (S.D. =28.62). Majority of the children i.e. 40 (41.67%) were undergoing hypertransfusion therapy at different centers; transfused red cells were in the range of 200-250 ml/kg annually. Only in 9 (9.37%) patients the red cell transfusion was more than 250 ml/kg/year. The red cell transfusion less than 150 ml/kg/year were in 12 (12.5%) patients (Table: 1).

Table 1: Total red cell transfusion in study group

Red cell transfusion (Ml/kg/year)	Number of patients	Percentage (%)
< 150	12	12.5
150 - 200	37	36.46
200 - 250	40	41.67
> 250	9	9.37
Total	98	100

Table 2 shows the red cell transfusion according the age of the child. A very important observation in this table was the requirement of red cells transfusion increases with age. The red cell volume transfused showed variation between different age groups. Red cell transfusion was higher in the age group of 25-30 years followed by 20-25 years age group. It was lower in the age group of 0-5 year (Table: 2).

Table 2: Red cell transfusion requirement according to the age group

Age group (years)	Mean red dell transfusion (ml/kg/year)

0 – 5	168.35
5 – 10	182.07
10 – 15	203.45
15 – 20	209.86
20 – 25	236.32
25 – 30	252.45

Iron overload and chelation: Iron overload in thalassemia patients was measured by serum ferritin levels. Out of 98 patients, 86 (89.58%) thalassemic children were on chelation therapy. Maximum numbers of patients 37 (38.54%) were on oral chelation therapy after this 35 (36.45%) patients on combined chelation therapy (Desferroxamine & oral chelation).

Only 14 (14.58%) were on parenteral (desferroxamine) chelation therapy. Out of 96 patients, 10 (10.41%) patients were not taking any chelation therapy. This table also shows mean red cell transfusion requirement which were minimum in desferroxamine chelation therapy group and maximum in patients those started chelation therapy but discontinued it and this difference was found highly significant (p<0.01). When the mean red cell transfusion requirement were compared from desferroxamine chelation therapy group to other group like oral chelation therapy group, combined chelation therapy group, group of patient started chelation therapy but discontinued it, difference was found highly significant (p<0.01).

When the mean red cell transfusion requirement were compared from oral chelation therapy group to other group like combined chelation therapy group, group of patient started chelation therapy but discontinued it, difference was found highly significant (p<0.01). The mean red cell transfusion requirement was highest in patients who started chelation therapy but discontinued it, when compared with combined chelation therapy group, the difference was found highly significant (p<0.01) (Table: 3).

Table 3: Type of chelation therapy

Type of chelation therapy		No. of patients (%)	Red cell transfusion requirement		'p' value
			Mean (ml/kg/ year)	S.D.	
Desferroxamine		14 (14.58%)	188.92	8.35	p < 0.01
Oral chelation		37 (38.54%)	207.86	12.27	
Combined therapy (Desferroxamine & oral chelation)		35 (36.45%)	196.65	10.15	
No chelation therapy	Not started	6 (6.25%)	174.87	6.37	
	Started but discontinued	4 (4.16%)	261.96	18.75	
Total		98 (100%)	201.20		

Conclusion: Red cell transfusion requirement & chelation therapy should be kept in mind in the patients receiving multiple transfusions. In present study the difference of mean red cell transfusion requirement among the all chelation therapy groups when compared with each other were found highly significant (p<0.01). The mean red cell transfusion requirement was minimum in combination therapy group (combination of two iron chelators such as parenteral desferroxamine plus oral deferiprone) and maximum in patients who started chelation therapy but discontinued it and this difference was found highly significant (p<0.01). Combination of two iron chelators (such as parenteral desferroxamine plus oral deferiprone) have been shown to produce additive and synergistic effects, may produce enhanced iron excretion, minimize side effects, decrease mean red cell transfusion requirement and improve compliance is strongly recommended in transfusion dependent thalassemia patients.

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