

Evaluation of iron overload and adequacy of packed red blood cells transfusion in children with thalassemia major

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ABSTRACT

Background: Transfusion therapy in patients with thalassemia major needs to address the common questions such as what should be the optimal hemoglobin (Hb) level for effective transfusion and how do transfusion requirements affect the success of iron chelation therapy. **Objective:** The objective of the study was to evaluate iron overload and adequacy of packed red blood cells (PRBCs) transfusion in children with thalassemia major along with the correlation of serum ferritin level with transfusional iron load and pre-transfusion Hb level. **Materials and Methods:** This single-center retrospective observational study was carried out in thalassemia day care center of tertiary care hospital for 1 year over 32 transfusion-dependent β -thalassemic patients up to 18 years of age. Data including pre-transfusion hemoglobin level, number and volume of PRBC transfused, and serum ferritin level for 1 year were analyzed, and annual transfusion iron load was calculated. Correlation of serum ferritin level with transfusional iron load and pre-transfusion Hb level was determined using Pearson coefficient (r) and p -value. **Results:** The mean pre-transfusion hemoglobin level was 6.4 ± 0.23 g%. The average number and volume of PRBCs transfused in a year were 12.5 ± 3.02 and 112 ml/kg, respectively, with the average annual transfusional iron load of $121.3 \text{ mg/kg} \pm 28.9$ or 0.3 mg/kg/day . A significant positive ($r=0.4184$, $p=0.017$) correlation was observed between serum ferritin level and transfusional iron load with the mean serum ferritin level of 1744 ± 604.6 ng/ml. Negative correlation was observed between serum ferritin and pre-transfusion Hb level ($r=-0.2624$ and $p=0.1537$). **Conclusion:** All patients were undertransfused and this undertransfusion further leads to more accumulation of iron in the body through increased absorption of dietary iron as a result of anemia and ineffective erythropoiesis.

Key words: Packed red blood cells transfusion, Serum ferritin, Thalassemia, Transfusional iron load

Beta-thalassemia major (β -TM) is a transfusion-dependent thalassemia (TDT) and requires regular blood transfusions (BTs) for the afflicted patients. Total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world [1]. In India, nearly 12,000 children with TM are born every year [1]. According to Thalassemia International Federation (TIF), only about 200,000 patients with β -TM are alive and registered and receive regular treatment around the world [1,2].

The recommended treatment for TM involves lifelong regular BTs usually at 2–5 weekly intervals to maintain pre-transfusion hemoglobin (Hb) level in the range of 9–10.5 g% [2]. This transfusion regimen promotes normal growth, allows normal physical activities, and adequately suppresses bone marrow activity in most patients and minimizes transfusional iron accumulation [3]. Iron overload occurs in these patients when iron intake is increased over a sustained period of time either as a result of repeated packed red blood cells (PRBCs) transfusion or increased absorption of iron through gastrointestinal tract (GIT).

In TDT, contribution of iron absorbed through GIT is small compared with transfusional iron load. Normal intestinal

iron absorption is about 1–2 mg/day. Patients who are poorly transfused, iron absorption through G.I. rises to 3–5 mg/day or more representing an additional 1–2 g of iron loading per year [2,4]. Various studies have evaluated adequacy and effectiveness of BTs in thalassemic patients [5–10]. In our country, thalassemic children are usually undertransfused [5–9]. This undertransfusion further leads to more accumulation of iron in the body through increased absorption of dietary iron as a result of anemia and ineffective erythropoiesis. Hence, chelation therapy might become inadequate and ineffective. Complications of iron overload are growth retardation, failure or delay of sexual maturation, involvement of heart (dilated cardiomyopathy), and liver and endocrinal glands. Thus, chronic BTs in thalassemic patients are double-edged sword requiring optimal transfusion with maximum benefit and minimum hazards.

Serum ferritin level is the most commonly employed test to evaluate iron overload in β -TM. The association between serum ferritin and levels of body iron is well established [11–13] and the test is easy to perform in comparison with the other tests for iron overload. The present study aims to evaluate iron overload and adequacy of PRBCs transfusion in children with TM along with

relationship between serum ferritin with transfusional iron load and pre-transfusion hemoglobin level. This will help to overcome various problems related to under- or over-transfusion along with initiation and follow-up of proper chelation therapy [14].

MATERIALS AND METHODS

This single-center retrospective observational study was carried out in thalassemia day care center of tertiary care hospital in Eastern Uttar Pradesh from April 2017 to June 2018 over transfusion dependent β -thalassemic patients up to 18 years of age. Patients with confirmed diagnosis of β -TM based on Hb variant test using high-performance liquid chromatography were included in the study. Patients of β -thalassemia trait (heterozygous), thalassemia intermedia, and α -thalassemia variant were excluded from the study. Approval for the study was obtained from the institutional ethics committee.

Children with confirmed diagnosis of β -TM were enrolled over initial 2 months. Data of patients were recorded in a pretested case record form including demographic profile and details of BTs including number, volume of PRBC transfused, pre-transfusion Hb level, and serum ferritin levels for 1 year. Newly diagnosed patients or patients whose previous 1 year data were not available were followed for 1 year to record the above parameters.

To assess the adequacy of BTs, we considered number and volume of PRBC transfused and mean pre-transfusion Hb level in a year. We calculated annual transfusional iron load (i.e., iron load due to only BTs) in milligram (mg) by the formula: (number of transfusions in a year X volume of PRBC transfused in one transfusion [mL/year] \times 60 \times 1.08) / (weight \times 100) as the hematocrit of transfused PRBC to be 60% and the estimated amount of iron per ml of PRBC to be 1.08 [2]. We correlated serum ferritin of these patients with the transfusional iron load and pre-transfusion Hb level.

Data were entered into Microsoft Excel spreadsheet and analyzed in the statistical package for Data Analysis version 2007 to determine the mean and standard deviations. The correlation of serum ferritin level with transfusional iron load and pre-transfusion Hb level was determined using Pearson coefficient (r) and p value.

RESULTS

A total of 33 children were enrolled for the study, of which one patient lost to follow-up. Data of 32 patients were recorded. Of 32 patients, 24 were male and 8 were female (male:female=3:1). The mean age of these patients was 6.0 ± 3.65 years and majority of the patients belonged to the age group of 4–6 years ($n=11$) followed by 7–10 years ($n=10$), as shown in Fig. 1.

Mean age at diagnosis was 13.25 ± 8.6 months with 68% of children diagnosed within the 1st year of life. Average weight of patients was 20.7 ± 9.72 kg. Of 32 patients, 6 patients (18.7%) were born of consanguineous marriage. All patients were undertransfused with mean pre-transfusion Hb concentration of 6.4 ± 0.23 g% which is persistent in almost all age groups. Average number of BTs in a year was 12.5 ± 3.02 . A total of

21 patients (65.6%) belonging to the age group of 4–6 years and 7–10 years were receiving monthly transfusion. With increasing age, frequency of transfusions also increased (Fig. 2).

The average volume of blood transfused was 112 ml/kg in a year (2502.3 ± 1632 ml in a year). Children in the age group of 13–14 years ($n=2$) received an average 148.5 ml/kg in a year (4608 ± 407.9 ml in a year) of BTs. Calculated average annual transfusional iron load was 121.3 ± 28.9 mg/kg or 0.3 mg/kg/day with maximum value of 160.3 mg/kg or 0.43 mg/kg/day in patients of age group 13–14 years (Table 1).

Mean serum ferritin level was 1744 ± 604.6 ng/mL. Serum ferritin of 6 (18.75%) children was <1000 ng/mL, 24 (75%) children was having level between 1000 and 2500 ng/mL, and 2 (6.25%) children was having >2500 ng/mL. Serum ferritin level was significantly higher in the age group of 11–12 years and 13–14 years as compared to the age group of 1–3 years ($p < 0.05$). There was a significant positive correlation between serum ferritin level and transfusional iron load ($r=0.4184$ and $p=0.017$) with coefficient of determination $r^2=0.1751$ (Fig. 3). Negative correlation was observed between serum ferritin and pre-transfusion Hb level ($r=-0.2624$ and $p=0.1537$), as shown in Fig. 4.

DISCUSSION

In our study group, a male preponderance of 75% (male-to-female ratio of 3:1) was observed. Only Indian studies have reported male preponderance (male-to-female ratio of 2.5:1) up to 70%

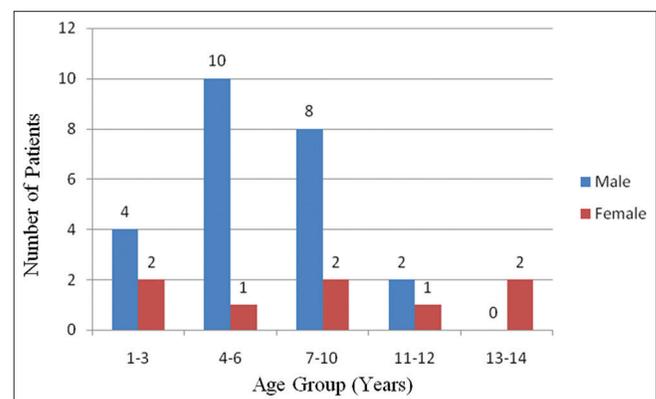


Figure 1: Age and gender distribution of children with β -thalassemia major ($n=32$)

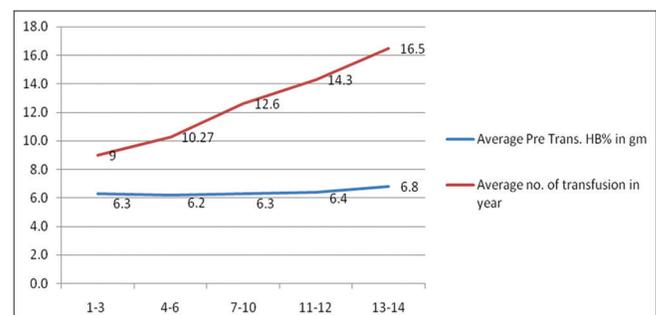
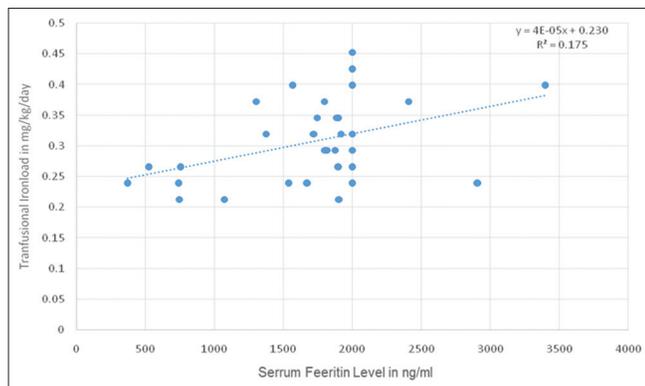
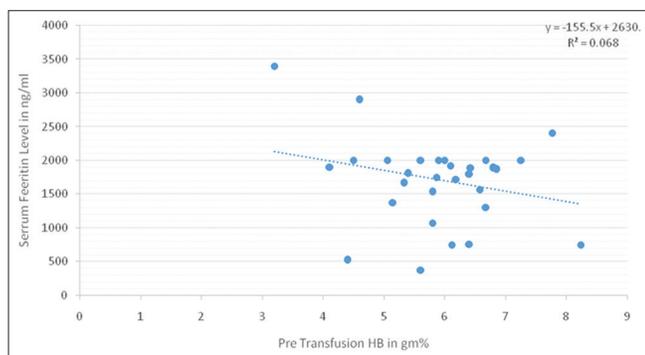


Figure 2: Average pre-transfusional hemoglobin level and average number of blood transfusions in different age groups

Table 1: Average number and volume of PRBCs transfused in 1 year along with calculated transfusional iron overload and measured serum ferritin level

Age group in years	Average weight in kg	Average Pre-trans. Hb (g%)	Average number of transfusion in year	Annual amount of PRBC transfused (hematocrit 60%) ml/kg	Volume of PRBC transfused in year (ml)	*Annual transfusion iron load in mg/kg/year	Daily iron loading in mg/kg/day	Mean serum ferritin level (ng/ml)
1–3	9.8	6.3	9	81	794.20	87.48	0.239	741
4–6	11.8	6.2	10.27	92.4	1104.70	99.85	0.273	1896
7–10	20.5	6.3	12.6	113.4	2350.60	122.47	0.335	1731
11–12	29.3	6.4	14.3	126	3654.00	136.08	0.372	2351
13–14	31	6.8	16.5	148.5	4608.00	160.38	0.439	2000
Average	20.5	6.4	12.5	112.3	2502.3	121.3	0.3	1744
St. dev.	9.72	0.23	3.02	26.81	1632.05	28.94	0.08	604.63

*Annual transfusional iron load (i.e., iron load due to only blood transfusion) in milligram (mg)

**Figure 3: Relationship between serum ferritin level and transfusional iron load****Figure 4: Relationship between serum ferritin level and pre-transfusion hemoglobin**

and 75% [8,15]. Male preponderance seen in India has been attributed to gender bias rather than an actual preponderance of disease in males. Mean age at diagnosis in our study was similar to the study done by Trehan *et al.* who observed mean age at diagnosis of 13.2±9.7 months with 64% of patients diagnosed within the 1st year of life [15].

Considering the TIF recommendation, our study showed that all children were undertransfused similar to the previous studies done by Sarkar *et al.* who found undertransfusion in 98.5% of children [6]. Shah *et al.* and Soni *et al.* showed nearly 53.5% and 48% of the patients were undertransfused [7,16]. Studies by Kumari *et al.* and Sarkar *et al.* showed mean pre-transfusion Hb of 7.89±1.77 and 7 g%, respectively, similar to our study [5,6]. Our study shows that the mean number of PRBC transfusion

in a year was 12.5±3.02 with majority (65.6%) of the patients getting monthly transfusion. This was similar to the studies done by Shah *et al.* and Mishra and Tiwari, where 62% and 55.6% of their patients, respectively, received monthly transfusion [7,8]. This frequency of BTs appears to be inadequate and need to be reviewed along with consideration for other relevant factors.

The average volume of PRBC transfused in our study was 112 ml/kg/year (2502.3±113 ml/year) while Thakor *et al.* found it to be 180.3 ml/kg/year [17]. According to IAP guidelines 2006, the average volume of transfusion should be 180 ml/kg/year in non-splenectomized patients. Hence, as per volume of transfusion, our children were undertransfused [18]. The rate of transfusional iron loading is relatively well defined in TM.

With the recommended transfusion scheme, patients usually receive between 100 and 200 mL of PRBCs/kg per year. This rate of transfusion is equivalent to 108–216 mg of iron/kg per year or 0.30–0.59 mg/kg per day [2]. Calculated average transfusional iron load in our study was within the lower normal range. Several studies (Worwood *et al.*, 1980; Cazzola *et al.*, 1983; and Aldouri *et al.*, 1987) have investigated the relationship between the magnitude of iron overload and serum ferritin concentration in β -thalassemia patients with transfusional iron overload [11,12].

The mean serum ferritin level for 1 year in our study was 1744±604.6 ng/mL with 81.5% of children having serum ferritin level >1000 ng/mL. The study done by Kumari *et al.* and Shah *et al.* also showed 82.4% and 93.7% of children, respectively, having serum ferritin level >1000 ng/mL [5,7]. Serum ferritin levels were significantly higher in the age group of 11–12 years and 13–14 years ($p < 0.05$) similar to the study done by Thakor *et al.* who also found high serum ferritin in the age group of 11–12 years [17]. A significant positive correlation of serum ferritin with transfusional iron load and negative correlation with pre-transfusional Hb was similar to the study found in Worwood *et al.* ($r = 0.41$ and $P = 0.001$) and Schettini *et al.*, respectively [12,19].

Limitation of our study is that serum ferritin is cumulative value of iron overload, whereas we have taken its pattern only for a year and we could not take other factors that might influence the levels such as dosing and compliance of chelation therapy since it was a retrospective study.

On the basis of the findings in present study we suggest that in TDT, adequate PRBC transfusion is needed to keep pre-transfusion

haemoglobin level between 9 - 10.5 gm% not only for optimal growth and physical activities but also to minimise further iron overload for effective chelation therapy.

CONCLUSION

In our study, all patients were undertransfused with persistent high serum ferritin level. Significant positive correlation of serum ferritin with transfusional iron load and negative correlation with pre-transfusion Hb level suggests that undertransfusion further leads to more accumulation of iron in the body through increased absorption of dietary iron as a result of anemia and ineffective erythropoiesis.

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