Clinical and Metabolic Complications in patients with thalassemia undergoing transfusion therapy

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ABSTRACT

Background: The transfusions in patients with thalassemia are a double-edged sword as the patients develop complications due to inadequate transfusions and due to multiple transfusions. These complications vary from metabolic complications such as diabetes mellitus and clinical complications such as growth retardation, transfusion-transmitted infections (TTIs), and iron overload. We selected Balasore district in Odisha which is a satellite center of AIIMS Bhubaneswar and has a huge population of hemoglobinopathy patients especially thalassemia and this district in Odisha lags in terms of healthcare and health awareness.

Materials and Method: In all, 123 patients with thalassemia major were included in this study for the evaluation of metabolic and clinical complications. Anthropometric measurements such as height and weight with age and gender were used for evaluation of growth parameters as per World Health Organization (WHO) reference data. Children were termed wasted and stunted if the values were below 2 standard deviation of the reference WHO median. Blood samples were collected for TTI status and fasting blood sugar levels.

Result: A total of 118 (95.9%) were detected to have under nutrition, 73 (59.3%) of the patients were HCV-positive, and 54 (48.6%) had high fasting blood sugar levels. Based on the HCV status, they were classified as HCV-positive and HCV-negative to compare the anthropometric and growth status in these patients. About 98.6% of the HCV-positive cases were undernutrition and 83.6% were stunted.

Conclusion: There is an increasing trend of associated metabolic derangements in patients with thalassemia. The district-level health services have an urgent need for improvement in chelation regimes and screening technologies.

Keywords: Metabolic, stunted, thalassemia, undernutrition

Introduction

Thalassemia is a group of disorders associated with a reduction in red blood cell production, anemia, and reduced hemoglobin levels. Beta thalassemia includes thalassemia major, intermedia, and minor. The burden of thalassemia in the tribal population of Odisha is huge especially in the districts of Balasore and Kalahandi.¹¹ Patients with thalassemia develop complications due to multiple transfusions and due to inadequate transfusions. Despite advances in treatments, complications such as excess iron overload, diabetes mellitus, transfusion-transmitted infections (TTIs), and short stature are seen in this group of patients. Primary care physicians (PCPs) play a vital role in general health maintenance including monitoring and screening for patients with thalassemia and implementation of national programs.

Patients with thalassemia major require regular transfusion therapy, but this treatment also carries a significant risk of acquired TTIs. Children with thalassemia major develop short stature despite advances in treatment. The causes of the short stature may be multifactorial including excess levels of iron in the body, endocrinal dysfunction such as diabetes mellitus, and acquired TTIs. This study was conducted with an objective to evaluate the growth pattern and the clinical and metabolic complications in patients with thalassemia undergoing transfusion therapy.

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Access this article online

Quick Response Code:

Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_845_19

How to cite this article: Raghuwanshi B, Kumari S, Sahoo DP. Clinical and Metabolic Complications in patients with thalassemia undergoing transfusion therapy. J Family Med Prim Care 2020;9:973-7.
Materials and Methods

Approximately 1000 patients with thalassemia major from Balasore district of Odisha were screened for clinical and metabolic complications of thalassemia. The study was conducted for 1 year from 2016 to 2017 at AIIMS Bhubaneswar.

The patients received irregular multiple transfusions at multiple centers. All those patients who received more than 5 packed red cells or whole blood transfusions were included in the study after ethical approval from the institutional ethical committee. The patient’s transfusion history, sociodemographic history, clinical parameters including anthropometric measurements, and blood samples were collected. The sociodemographic characteristics such as age were recorded from school records/birth records. The anthropometric measurements such as height and weight were recorded by measuring tape and weighing machine. The weighing machine was calibrated to zero and the patients removed shoes before weighing.

World Health Organization (WHO) reference data for age and sex to get the height for age and weight for height indices were used. Children below 2 standard deviation (SD) of the reference median on any of these indices were considered as undernourished and termed as stunted and wasted, respectively. WHO anthropic calculator was used to calculate the Z-score for height for age and weight for height for under-5 children.\(^5\) WHO growth reference data for 5–19 years were used to calculate BMI-for-age for both boys and girls to assess wasting and length for age to assess stunting.\(^6,8\) Z-score less than 2 SD for BMI for age was termed as wasted and height for age less than 2 SD for height for age was termed as stunted.\(^9\)

The blood samples were collected for evaluation of TTI status. The data were thus obtained including the clinical examination results including anthropometric measurements and laboratory results and these were subsequently analyzed.

The data were entered in a Microsoft Excel 2010 worksheet. Data were cleaned and analyzed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA).

Results

A total of 123 patients with major beta-thalassemia were enrolled in this study. The mean age of patients was 9.5 ± 5.2 years. About 82 (66.7%) and 41 (33.3%) of the participants were male and female, respectively. The majority of the participants were in the age group of 5–9 years. [Table 1].

Growth retardation

Anthropometry is a useful tool, both for monitoring growth and for nutritional assessment. The anthropometric measurements including weight and height were used to identify the physical condition of children. Out of the total 123 patients, 118 were detected to have undernutrition [Table 2] which is more prevalent in HCV-positive cases, that is, 72 of 73 (98.6%) with an odd’s ratio of 6.261, \(P = 0.067\).

Out of the 123 patients, 13 HCV-positive cases (17.8%) were found wasted as per the WHO of weight for age (<80% of W/A) and 14 HCV-negative participants also found wasted (28.0%) [Table 3]. The majority of the patients with thalassemia (61/73, i.e. 83.6% HCV-positive and 41/50, i.e. 82.0% HCV-negative) were found stunted as per the WHO guidelines of height for age. While 15.1% HCV-positive cases and 24.0% HVC-negative cases were lagging behind in both weight/age and height/age, that is, they were both wasted and stunted. Thus, a high proportion of the patients show growth retardation, which may be due to iron deposition in the pituitary gland; another consequence of inadequate chelation and high ferritin levels.

Prevalence of TTIs

Among various TTIs, hepatitis C and HIV were prevalent among 59.3% and 4.1% of the study participants, respectively. None of the study participants tested positive for HBsAg, parvovirus, syphilis, and malaria.

A striking 59.3% of the patients were HCV-positive which is significantly more than the prevalence in general population (\(P < 0.001\)). The prevalence of HIV positivity is not statistically significant compared with the general population. However, the data available from National AIDS Control Organization (NACO) and voluntary blood donor studies include only adolescents and adults, while our study includes patients with thalassemia major who were under 18 years of age.

Because a large proportion of patients were HCV-positive, we analyzed our data by finding correlation between:

(1) HCV positivity and age

With age the number of blood transfusions received increases and so does the risk of acquiring TTIs. There is a linear relationship between age and HCV positivity which indicates that the more the age of the patient, the more the chance of him or her being HCV-positive.

In India, mandatory screening for HCV was introduced in 2002. It therefore follows that thalassemic children born in 2002 or later should...
not ideally be HCV-positive. However, out of the 73 patients who are HCV-positive, 46 patients (46/123 (37.39%) are below 9 years of age and 24 patients are below 14 years of age (24/123 (19.51%). A total of 70 HCV-positive patients are below 14 years of age (56.91%) and all these patients received HCV screened blood. In all these HCV-positive cases, the causal role of blood transfusion can only be logically established by documenting the absence of HCV infection in mothers before or during pregnancy. There are a total of 105 children who are below 14 years of age, and out of them 70 children, that is, 70 of 105 (56.91%) are HCV-positive despite the fact that the blood they received was subjected to screening for HCV.

The proportion of hepatitis C was higher among study participants of younger age and was significantly associated with age ($P < 0.05$) [Table 4].

(II) Diabetes:

In this study, HCV-positive participants had a higher proportion of high blood sugar [Table 5] levels, that is, 38 of 73 (52.3%) than HCV-negative patients, that is, 22 of 50 (43.5%) with an odd's ratio of 48.6%. Further data analysis revealed that 28 of 50 (56.5%) of HCV-negative patients had normal blood sugar levels suggesting the fact that patients with thalassemia with raised blood sugar levels are due to increased iron load and inadequate chelation therapy. This is in accord with the fact that diabetes in these patients is usually due to iron deposition in the pancreas leading to insulin deficiency. We performed fasting blood sugar testing of all the 123 patients to detect impairment in glucose levels. However, we could not perform serum ferritin levels due to cost constraints.

### Table 2: Distribution of undernutrition cases in HCV-positive and -negative patients with thalassemia

| HCV          | Total | Odds ratio | CI          |
|--------------|-------|------------|-------------|
| Undernutrition | Positive | Negative |             |
| BMI Normal | Count | 72 | 46 | 118 | 6.261 | 0.6785, 57.77 |
| % | 98.6% | 92.0% | 95.9% |
| BMI Total | Count | 73 | 50 | 123 |          | |
| % | 100.0% | 100.0% | 100.0% |

Chi square=3.345, $P=0.067$

CI: confidence interval; BMI: body mass index

### Table 3: Distribution of growth retardation in HCV-positive and -negative patients with thalassemia

| HCV | Total | Odds ratio | CI          |
|-----|-------|------------|-------------|
| Wasted | Positive | Negative |             |
| Yes | Count | 13 | 14 | 27 | 0.557 | 0.2356-1.317 |
| % | 17.8% | 28.0% | 22.0% |
| No | Count | 60 | 36 | 96 |          | |
| % | 82.2% | 72.0% | 78.0% |
| Total | Count | 73 | 50 | 123 |          | |
| % | 100.0% | 100.0% | 100.0% |

Chi-square=1.799, $P=0.180$

### Table 4: Distribution of growth retardation in HCV-positive and -negative patients with thalassemia

| HCV | Total | Odds ratio | CI          |
|-----|-------|------------|-------------|
| Stunted | Positive | Negative |             |
| Yes | Count | 61 | 41 | 102 | 1.116 | 0.431-2.887 |
| % | 83.6% | 82.0% | 82.9% |
| No | Count | 12 | 9 | 21 |          | |
| % | 16.4% | 18.0% | 17.1% |
| Total | Count | 73 | 50 | 123 |          | |
| % | 100.0% | 100.0% | 100.0% |

Chi square=0.051, $P=0.821$

| Both wasted and stunted | yes | Count | 11 | 12 | 23 | 0.561 | 0.225-1.399 |
| % | 15.1% | 24.0% | 18.7% |
| no | Count | 62 | 38 | 100 |          | |
| % | 84.9% | 76.0% | 81.3% |
| Total | Count | 73 | 50 | 123 |          | |
| % | 100.0% | 100.0% | 100.0% |

Chi square=1.557, $P=0.221$

CI: confidence interval
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Table 4: Hepatitis C and its association with the sex and age of patients with thalassemia

| Sex  | Negative | Positive | P    |
|------|----------|----------|------|
| Male | 33       | 49       | 0.897|
| Female | 17   | 24       |      |
| Age groups (years) | | | |
| <5 | 5        | 18       | 0.005|
| 5-9 | 14       | 28       |      |
| 10-14 | 16      | 24       |      |
| 15 and above | 11 | 3        |      |

Table 5: Proportion of patients with high blood sugar levels in HCV-positive and -negative thalassemia cases

| HCV | FBS | DM | Positive | Negative | Total | Odds ratio | CI      |
|-----|-----|----|----------|----------|-------|------------|---------|
|     | Count | % | Count | % | Count | % |        |        |
| FBS | 34 | 52.3% | 20 | 43.5% | 54 | 48.6% | 1.426 | 0.6672 |
| DM  | 31 | 47.7% | 26 | 56.5% | 57 | 51.4% | 3.047 |        |
| Total | 65 | 100.0% | 46 | 100.0% | 111 | 100.0% |        |        |

Chi square=0.841, P=0.359
CI: confidence interval

Discussion

The complications of thalassemia are a major cause of concern as thalassemia is a major public health problem in India. The Balasore district of Odisha has a high prevalence of hemoglobinopathy patients especially thalassemia. The lack of awareness and educational and screening programs in districts and among the tribal population are reflected by the fact that the majority of patients in the study were under 14 years of age. There is a need for the importance of carrier screening programs by primary healthcare physicians to educate the people especially the target groups with thalassemia minor trait and asymptomatic individuals so that they are informed and understand their reproductive risks and options. The carrier screening programs by primary healthcare physicians accompanied by counseling can help in reducing the burden of disease by providing information to target groups regarding personal health and potential health of their offspring. Imparting education by annual thalassemia meet or thalassemia day with specific news updates for the target population can bring long-term changes in disease management. This is a vital goal that can be achieved with the dedicated efforts of PCPs.\[7,8\]

The PCP can play an important role from the initial screening, diagnosis and regular monitoring of the patient for treatment and complications. The PCP is a vital alliance between the patient and treating specialists especially at district levels where specialist care is not available. The complications seen in a majority of patients with thalassemia in our study may be due to multiple factors such as poor socioeconomics, poor knowledge and access to healthcare services, less outreach of national programs benefits, unavailability of specialist care, and lack of timely monitoring and treatment of complications. As a severe lacuna in healthcare services exists at district levels, therefore the importance of PCP in management of chronic diseases becomes very important as this is the link which provides a continuous, coordinated, and comprehensive care.\[6\]

In our study, 118 patients were found to have stunting and wasting, which is more prevalent in HCV-positive cases, that is, 72 of 73 (98.6%) with an odd’s ratio of 6.261, \(P = 0.067\). Out of the 83.6%, HCV-positive (61 patients) were stunted and 17.8% HCV-positive (13 patients) were wasted. Thus, a high proportion of the patients show growth retardation, which may be due to iron deposition in the pituitary gland, which another consequence of iron chelators and high ferritin levels along with a nutritional deficiency in these patients. The current practice is to begin iron chelation therapy when the serum ferritin levels reach 1000 ng/mL or when the child is >2 years of age or has received about 10–20 transfusions. Inadequate iron chelation in developing countries, like India with poor socioeconomic background compounds the problem of the accumulation of excess iron within tissues and progressive organ damage and endocrine dysfunction. Early initiation of therapy of iron chelation to improve chelation for better growth and sexual development and reduced toxicity will be beneficial. Deferasirox is a promising once-daily oral therapy for the treatment of transfusional iron overload.

The cause of stunting in patients with thalassemia is multifactorial and not well-understood. Iron overload, intensive use of iron chelators, and gonadal damage may all contribute to stunting though the individual and relative contribution of each factor are not known. Timely and adequate follow-up of patients with thalassemia for transfusion therapy and iron chelation therapy leads to a reduced risk of stunting and better endocrine development.\[9,10\]

Our study participants exhibited a myriad of complications of treatment therapy including TTIs, stunting, wasting, and high sugar levels. HCV positivity was seen in 59.3% (73) of patients although screening for HCV became mandatory since the year 2002 and despite the fact that 56.91% HCV-positive (70 patients) received blood which was subjected to HCV screening. Therefore, the screening methodology, kits, and so on used require evaluation and validation. With such high TTI positivity, the screening methodologies which have a short window period may be given a priority. Second, there is a high prevalence of HCV in thalassemia as HCV virus has a long window period for antibody development, and therefore the introduction of better screening methodologies that facilitate shorter window period detection is a dire need.\[9,11\]

The complications in patients with thalassemia seen in our study due to inadequate transfusions and due to transfusion therapy included growth retardation, high HCV positivity, and high blood glucose levels. Therefore, more consistent efforts to improve
chelation regimes and better screening methodology are required. It is therefore advisable to develop and streamline the transfusion protocols so that patients receive adequate transfusion and adequate chelation to reduce the complications in thalassemia.

**Conclusion**

The management of these multiple complications requires a continuous, coordinated, and comprehensive care by PCP especially at district levels where there is scarcity of health specialists. The inferior quality of care reemphasizes the role of PCPs in the screening, treatment, and monitoring of complications of patients with thalassemia. The district-level healthcare facilities need reorganizations for better management of chronic disease management programs.

**Financial support and sponsorship**

Intramural grant.

**Conflicts of interest**

There are no conflicts of interest.

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