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Original Research Article

Pulmonary Function and Hematological Characteristics in Children with Thalassemia Major

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Abstract:

Background: Insufficient production of the haemoglobin chains causes persistent hemolytic anaemia in people with thalassemia, a series of recessively inherited illnesses. The exact source of pulmonary function problems after iron overload from repeated blood transfusions is unknown.

Methods: The pulmonary function of transfusion-reliant children with thalassemia was evaluated and compared to that of typically developing children in this case-control study. For this study, 35 kids were selected at random. Serum ferritin levels were examined for their possible links to pulmonary dysfunction.

Results: The study found that the ages at which thalassemia patients began receiving transfusion therapy ranged from 1.5 months to 70 months, with a median of 8 months. Haemoglobin levels before transfusion ranged from 6.8 to 11.4 gm%, on average hovering around 8.5 gm%. There was a wide range from 850 ml to 37,200 ml of blood transfused. The average serum ferritin concentration was 2000 ng/ml last year. Patients on chelation therapy for an average of 4.7 years. Although most pulmonary function test (PFT) measures were within normal ranges when comparing thalassemia cases and controls, PEF 25%-75% was considerably lower in thalassemia-affected children.

Conclusion: This study reveals the prevalence of pulmonary dysfunction, especially in a restrictive lung pattern, in thalassemia patients, although these individuals may not exhibit clinical symptoms of pulmonary dysfunction. Multiple causes contribute to the disease's development, including excessive blood transfusions, chelation therapy, and iron overload. More study is required to understand the causes and develop effective strategies for avoiding problems.

Keywords: Thalassemia, Pulmonary Function, Iron Overload, Restrictive Lung Pattern, Chelation Therapy, Complications.

Introduction

Thalassemia refers to a collection of diseases inherited in a recessive fashion. It's caused by a deficiency in the patient's red cells' ability to produce the - or - chain of Haemoglobin [1]. The result is chronic hemolytic anaemia due to a lack of Haemoglobin and secondary red cell abnormalities due to a comparative excess of the other, unaffected globin chain.

Most third-world countries rely heavily on regular blood transfusions as the backbone of treatment. Long-term transfusion therapy always results in hemosiderosis unless proper chelation therapy is implemented [2].

Several studies of people with thalassemia have shown restrictive obstructive lung disease, lung disease, and diffusion anomalies [3]. However, the root of pulmonary function issues is unclear. In most investigations, serum ferritin levels have shown mixed outcomes when correlated with pulmonary function tests. There seems to be a lack of information from India on this topic. This research aimed to examine the relationship between serum ferritin levels and pulmonary function impairments in thalassemia patients.

Objectives

1. To study pulmonary function tests in transfusion-dependent children with β thalassemia.
2. To compare pulmonary functions in transfusion-dependent β thalassemia children with normal children.

Review of Literature

The maximum severe form of congenital hemolytic anaemia is beta thalassemia major, often known as Cooley's anaemia. As it develops during the

transition from HbF to HbA, it often appears between the fourth and sixth months of pregnancy.

Molecular pathogenesis: Thalassemias are inherited as autosomal codominant diseases caused by various molecular abnormalities [4]. Haemoglobin A (HbA), the form of Haemoglobin seen in adults, is a tetramer of two chains. Chains are fixed by a single globin gene on chromosome 16, while chains are encoded by two-login genes placed in tandem on chromosome 11. Thalassemia-causing mutations occur most frequently in people of Mediterranean, African, and Asian descent. Depending on the patient's inherited alleles, a wide range of clinical manifestations might exist.

Morphology: Patients with thalassemia major have more prominent microcytosis and hypochromia in their smears. Like other hemolytic anaemias, thalassemia majorly causes physical alterations to the body, but on a much larger scale [5]. Dramatic hyperplasia of erythroid progenitors, with a shift towards initial forms, is the combined outcome of inefficient erythropoiesis and hemolysis. Extramedullary hematopoiesis causes noticeable splenomegaly, hepatomegaly, and lymphadenopathy, while an enlarged erythropoietic marrow can lead to skeletal abnormalities [6]. Severe hemosiderosis develops if measures are not taken to prevent iron overload.

Clinical course: Postnatally, as HbF synthesis declines, the symptoms of thalassemia major become apparent. Affected children do not thrive after birth and show signs of delayed development. Blood infusions are their only source of sustenance, as they cure their anaemia and lessen the skeletal abnormalities caused by excessive erythropoiesis [7]. It's conceivable to live into your 2^{nd}or 3^{rd} decade with blood transfusions, but iron excess will eventually set in. Iron overload is a natural consequence of receiving a transfusion of red cells and the average daily intake of iron from food. These disorders include those linked with inefficient erythropoiesis, in which the negative regulator of iron uptake, plasma hepcidin, is under expressed [8,9].

The results of a study conducted by [10] on pulmonary function testing (PFT) in transfusion-dependent thalassemic children showed the following: of 40 patients with thalassemia major, 20% had normal PFT, while the remaining 50% had abnormal PFT, with 18% showing restrictive PFT and 10% showing obstructive PFT. The PFTs of all 40 controls were within the normal range.

In a 2019 study [11], 21 of the 34 individuals were male, whereas 13 were female. There was no statistically significant relationship between the participants' mean serum ferritin levels (3610.822679.51ng/mL) and their ages, number of years of transfusions, or number of years of chelation. Boys' lung capacity was shown to be less than that of girls in terms of both forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1%). With considerable involvement in 73.5% of cases (FEV1 80%), the PFT indicated a restrictive pattern in the study group (FEV1/FVC=>0.7). Age was found to negatively correlate with FEV1% ($r = -0.5077$, $P = 0.01$), thus emphasising the significance of the length of time that iron excess was present. The serum ferritin level was negatively correlated with restrictive lung disease ($r = - 0.06$, $P = 0.75$). However, this link was not statistically significant. The iron levels in the hearts, pancreas, and livers of 76 thalassemia major (TM) patients were compared with pulmonary function tests (PFTs) [12]. Some sixteen per cent had a restrictive pulmonary illness, thirty-two per cent had hyperinflation, and three per cent had inadequate diffusing capacity. There were signs of minor airway illness and air trapping, but no patients satisfied airway blockage criteria defined by the Global Initiative for Chronic Lung illness. There was no connection between PFTs and iron overload in the body. Inflammation was linked to restrictive lung disease. They determined that pulmonary abnormalities in TM patients indicated the small airways' blockage. Fewer people suffer from illnesses that restrict movement or hinder diffusion.

Methodology

Study Population: Participants were children with a confirmed diagnosis of thalassemia major who received routine transfusions at the Pediatric department of Darbhanga Medical College and Hospital. Jesus & Mary Academy, Darbhanga children of similar age and gender served as controls. The parents gave their permission after being fully informed of the risks involved.

Method of Collection of Data

Inclusion Criteria

- Children who have received a positive thalassemia diagnosis
- People older than three
- They were the same age and gender as typical kids

Paediatric patients at Darbhanga Medical College & Hospital, Laheriasarai, Darbhanga, Bihar, who have thalassemia and are receiving regular blood transfusions, with or without iron chelation therapy, are studied.

Exclusion Criteria

- Youngsters are affected by respiratory disorders.
- Cardiac Arrest

Methods

Children who met the study's inclusion requirements were chosen. All patients and controls had their parents give their informed consent. Patients' demographic information, including their age at diagnosis, the age of their first blood transfusion, the total number of blood transfusions they've had, the length of time they were on iron chelation therapy, their pre-transfusion haemoglobin levels, their mean ferritin levels from the previous year, and the results of their physical examinations, were entered on a proforma.

A spirometer test was performed to evaluate lung function within 3 days of receiving a blood transfusion. The spirometry data included the following measurements: forced vital capacity (FVC), (FEV1), Peak Expiratory Flow Rate (PEFR), mid-peak expiratory flow (PEF25%-75%), and forced expiratory volume in one second (FEV1/FVC). The pulmonary function tests were performed three times, with the averages being used in the analysis. Measurements of serum ferritin were made. The haemoglobin count was calculated mechanically.

Design of the Study

Study comparing children with thalassemia to healthy children of the similar gender and age.

Sample Size

Between people with thalassemia, the mean forced vital capacity (FVC) is about 79.6 (SD15.4), while it is 91.7 (SD9.5) in healthy people, according to a review of the relevant literature. It was anticipated that about 35 people were researched in each group to have 80% power and 5% alpha error in estimating the differences above.

Statistical Methods

Quantitative characteristics such as FVC, FEV1, PEFR, and serum ferritin were compared using descriptive statistics (median, mean and standard deviation).

The parameters of the pulmonary function tests were compared between the patients and controls using the student's t-test. Serum ferritin levels, total blood transfusion volume, and chelation therapy duration were correlated with pulmonary function test parameters using Pearson's Correlation analysis. The statistical threshold for significance was set at a probability value of less than or equal to 0.05.

Result

From October 2018 through September 2020, the Paediatric Department at Darbhanga Medical College & Hospital tested the pulmonary function of 35 thalassemia primary children receiving frequent blood transfusions with or without iron chelation therapy.

We ruled out any kids who suffered from respiratory or cardiac conditions. Thirty-five healthy youngsters of similar age and gender had PFT for evaluation.

Table 1: General Characteristics of Control and Cases

	Control N(35) Mean ± SD	Cases N (35) Mean ± SD
Age (yrs)	**9.11±3.36**	**9.11±3.36**
Wt. (kgs)	**27.69±9.99**	**23.66±6.98**
Ht. (cms)	**133.46±18.35**	**123.63±14.36**
Sex- Males	**18**	**18**
Females	**17**	**17**

The sample's aggregate data are summarised in Table 1. Of 35 kids, 18 (51%) were boys and 17 (49%) were girls. Children's ages ranged from three to sixteen, with nine years being the median. Weights for the control group ranged from 15 to 53 kilogrammes (mean SD: 27.69 9.99) and for the case group, 15 to 46 kilogrammes (mean SD: 23.66 6.98). The heights of the control group ranged from 100 to 175 centimetres (mean SD: 133.46 18.35), while those of the patients ranged from 100 to 155 centimetres (mean SD: 123.63 14.36).

Table 2: Haematological characteristics of thalassemia cases

	Median (Range)	Mean ±SD	95% CI	Interquartile Range
Age at start of transfusion(months)	8.000(1.5-70)	16.41 ±16.07	10.89-21.93	24
Pre- transfusion Hb (gm %)	8.50(6.8-11.4)	8.56 ± 1.14	8.16-8.95	2
Cumulative amount of transfusion(ml)	13650.00(850-37200)	15018.33 ±8084.17	11999.65-18037.01	9225
Serum ferritin (ng/ml) preceding 1 yr	2000.00 (435.5-9522)	2719.757 ± 1909.92	2063.670-3375.83	1888.5
Duration of chelation therapy (yrs)	4.700(0.0-10)	4.243 ±2.83	3.184-5.30	4.7
Age at start of chelation therapy(yrs)	3.6(1-9)	3.757±2.23	2.923-4.59	3

Table 2 shows the hematological characteristics of thalassemia children. Age at the start of transfusion therapy ranged between 1.5 -70 months (median 8 and means 16.414±16.07).

Pre-transfusion haemoglobin ranged between 6.8-11.4 gm.% (median 8.5and mean±SD 8.563 ± 1.14). The cumulative amount of blood transfusion, i.e., the total amount received, ranged between 850-37,200ml (median 1365 mean ± SD of 15018.33± 8084.17). Serum ferritin levels ranged between 435.5 - 9522.0 ng/ml (median 2000.00 and mean±SD 2719.75±1909.92). 32 children received iron chelation therapy.

The age at which chelation therapy started ranged between 1-9 yrs (median 3.6 and mean±SD 3.757±2.23). Duration of chelation therapy ranged between 0.40 -11 yrs (median 4.7 and mean±SD 4.243±2.83).

Table 3: Comparison of PFT parameters among controls and cases

PFT Parameters	Control Mean±SD n-35	Cases Mean±SD n-35	p-value
FEV_1(% pred)	90.74±16.92	96.06±41.58	0.06
FVC (% pred)	89.37±17.57	114.43±77.30	0.486
FEV_1/FVC	99.40±8.041	92.57±20.09	0.066
PEFR (% pred)	108.71±93.47	91.97±62.23	0.381
PEF (25%-75%)	84.34±26.77	69.34±27.06	0.023*

Parameters of the PFT are compared in Table 3 for easy viewing. Patients of both sexes were included in the study, and all PFT measures were within the normal range and showed no statistically significant changes between cases and controls. PEF25%-75% was considerably lower in children with Thalassemia, but in the control group, it was within the normal range (84.34 26.77).

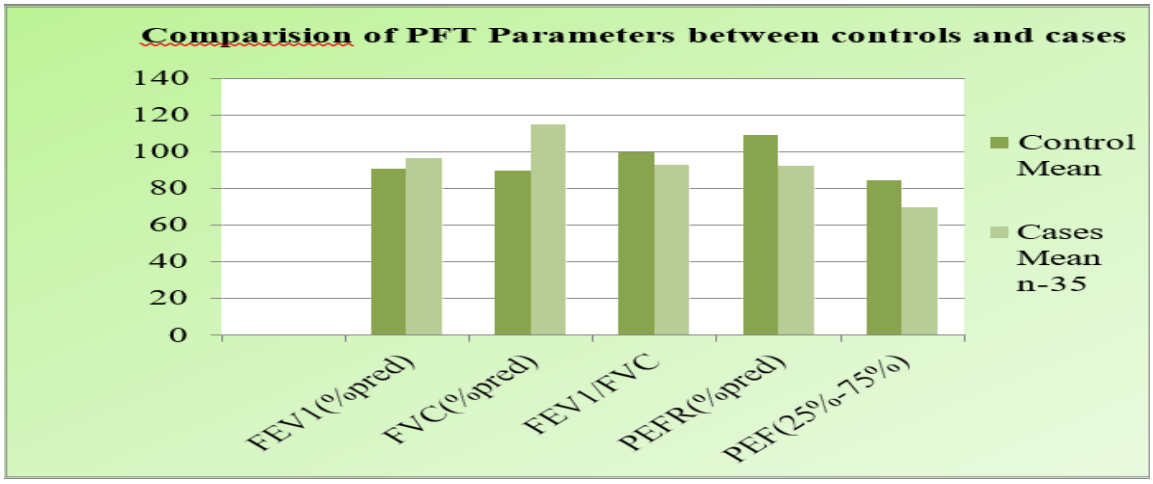

Figure 1: Evaluation of PFT Parameters between Controls and Cases

Table 4: Correlation of PFT Parameters with Cumulative Blood Transfusion

PFT Parameters	Mean ±SD	Cumulative blood transfusion	
		R	P
FEV1 (%pred)	**96.06 ± 41.58**	**-0.202**	**0.238**
FVC (%pred)	**114.43 ± 77.30**	**-0.278**	**0.101**
FEV1/FVC	**92.57 ± 20.09**	**0.135**	**0.431**
PEFR (%pred)	**9.97 ± 62.23**	**-0.276**	**0.103**
PEF (25%-&75%)	**69.34 ±27.06**	**0.162**	**0.345**

Correlation is significant at 0.05 level (2-tailed) Correlation is very significant at 0.01 level (2-tailed)

PFT values and total blood transfusions are correlated in Table 4. FEV1 (r = -0.202, p= 0.238), FVC (r = -0.278, p= 0.101), and PEFR (r = -0.276, p= 0.103) were all shown to be negatively correlated with cumulative blood transfusion. But had no statistically significant relationships with either FEV1/FVC (r = -0.135, p= 0.431) or PEF (25%-75%), (r = -0.162, p= 0.345).

Discussion

Important new information about how children with thalassemia major breathe and how this study has uncovered their blood looks.

The clinical profile of the thalassemia group can be better understood by analysing haematological

parameters such as age at the commencement of transfusion therapy, pre-transfusion haemoglobin levels, cumulative blood transfusion volumes, serum ferritin levels, and length of chelation medication. The wide range of values for these criteria indicates the diversity of the thalassemia community as a whole.

Most of the examined parameters for pulmonary function among children with thalassemia were within the normal range, as determined by pulmonary function tests (PFTs). This is a promising result since it suggests that the illness may not adversely impair the pulmonary function of these youngsters, at least in the absence of clinical symptoms. PEF between 25% and 75% was much lower in the thalassemia group, though, so that's something to keep in mind. A decrease in peak expiratory flow within this range may indicate small-airway dysfunction and air trapping in these patients.

A correlation study was conducted to learn more about the factors associated with thalassemia and their impact on pulmonary function. Blood transfusions inversely correlated with pulmonary function tests (FEV1, FVC, and PEFR). These associations were not statistically significant, but they do raise the possibility that the more the frequency with which a child receives transfusions, the more significant the effect on lung volume. However, positive associations were observed between FEV1/FVC and PEF (25%-75%), albeit not statistically significant. The results of this study provide clues about the intricate interplay between iron excess, chelation therapy, and pulmonary function in thalassemia patients.

This study thoroughly evaluates Children with thalassemia major's haematological and pulmonary features. Most measures of pulmonary function were within normal limits, although a 25%-75% drop in PEF warrants close monitoring and consideration of treatments to correct small-airway dysfunction. The relationship between pulmonary function and parameters such as cumulative blood transfusion is further highlighted by the need to manage iron overload and optimise chelation therapy to maintain lung health in thalassemia patients. Confirming these results and developing more specific management options for this patient population requires more study and larger-scale investigations.

However, several investigations have found no difference in pre-transfusion haemoglobin levels between sexes [13]. In another research investigation, both normal and impaired pulmonary function in thalassemic youngsters was assessed independently. Children with thalassemia anaemia have been reported to have lower haemoglobin levels. Our study quantified iron stores using total blood transfusions (mean SD: 15018.338084.17). Overload, whereas other research has estimated the number of transfusions over time. Our study found that serum ferritin levels were similar to those in prior research (mean SD: 2719.751909.92). Patients undergoing chelation showed a decreased ferritin load. In our study, all but three kids were treated with iron chelation. Despite chelation therapy, serum ferritin levels remained elevated. [14] have all researched serum ferritin levels. [15] Ferritin levels were significantly greater in thalassemic children with impaired pulmonary function (2,1,13). All the kids in our study were given chelating agents and transfusions regularly.

Conclusion

Each member in the series had no obvious lung illness symptoms. Rarely do thalassemia patients have breathing problems. To date, we don't know the whole clinical significance of pulmonary disease in TM. In this study's functional evaluation, thalassemia major patients had a considerably reduced FEF25%-75%, an indicative of small-airway disease that traps air. Some Thalassemia patients reported restricted and obstructive PFTs. Our data suggest several pathogenic causes for pulmonary dysfunction in thalassemia, such iron overload, blood transfusion, chelation, and others. We cannot now identify the source of pulmonary dysfunction. Chronically accumulating hemosiderin, or free iron, in organs and tissues may be the main cause of free radical mediators of oxidative damage, which accelerates disease onset.

Thus, more research is needed to elucidate Thalassemia-related lung impairment. Standardised therapy will improve thalassemics' health and happiness. These findings suggest that thalassemia patients with better iron chelation and supervision may live virtually normal lives.

Limitations of the Study

Better results could be attained with a bigger sample size. However, the investigation is complicated by the absence of clinical data. Since we lacked the equipment to test DLCO, TLC, or RV, we could not establish any correlation between these quantities and iron burden/overload.

Future Directions of the Study

The relationship between serum ferritin levels and pulmonary function tests in patients with thalassemia of varying ages. Hepatosplenomegaly and the results of lung function tests. Third, the thalassemic patient's age correlates with the outcomes of pulmonary function tests. Serum ferritin correlation with patient age and abnormal PFT.

Serum ferritin levels were compared in thalassemic patients with normal and abnormal PFT results.

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