Original Article

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Physiology Section

Study of Pulmonary Function Tests in Multitransfused Children with Thalassaemia: A Case-control Study

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ABSTRACT

Introduction: Lung involvement is one of the known complications of thalassaemia. This study was undertaken to assess the predominant type of pulmonary dysfunction. Most studies show pulmonary function abnormalities but the results are conflicting.

Aim: To study Pulmonary Function Tests (PFTs) in multitransfused children with thalassaemia and compare them with normal children.

Materials and Methods: This was a case-control study conducted from May 2012 to June 2013 at MS Ramaiah Medical College, Bengaluru, Karnataka, India, which included 35 children in the age group of 3-16 years with β-thalassaemia major and on regular transfusion as cases and 35 age and sex matched healthy children participated as controls. PFTs were done in 35 children with β-thalassaemia major, using Spirobank G and within three days of blood transfusion. Following parameters were recorded: Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 second (FEV1), Ratio of Forced Expiratory Volume in 1 second to Forced Vital Capacity (FEV1/FVC), Peak Expiratory Flow Rate (PEFR), and Forced Expiratory Flow (FEF 25-75%). Student's' test was used for statistical analysis.

Results: Percentage abnormalities of PFT in thalassaemia children were observed, 20 (57.14%) children had normal PFTs. Among the remaining children 9 (25.71%), 5 (14.29%) and 1 (2.86%) had restrictive, obstructive and mixed pattern of abnormalities, respectively.

Conclusion: Pulmonary function appeared to be affected in a majority of subjects with thalassaemia. Abnormal patterns of lung function were common in which restrictive type was predominant. No respiratory symptoms was found in any of these children. Studies are needed to establish the precise cause of pulmonary dysfunction.

Keywords: Forced vital capacity, Forced expiratory flow, Peak expiratory flow rate

INTRODUCTION

Thalassaemias are a heterogeneous group of inherited disorders caused by mutations that decrease the rate of synthesis of alpha and beta chains. As a consequence, there is a deficiency of haemoglobin, with additional secondary red cell abnormalities caused by the relative excess of the other unaffected globin chain and chronic haemolytic anaemia [1].

Beta thalassaemia major also termed Cooley's anaemia, is the most severe form of congenital haemolytic anaemia. It results from the abnormal synthesis of the β-chain haemoglobin; thus it usually starts to manifest as early as 4-6 months of prenatal life during the switch from HbF to HbA [2]. Anatomic changes in β-thalassaemia major are similar to those seen in other haemolytic anaemia's but in extreme degree. The combination of ineffective erythropoiesis and haemolysis results in a striking hyperplasia of erythroid progenitors, with a shift toward early forms. The expanded erythropoietic marrow may produce skeletal deformities and the extramedullary haematopoiesis results in prominent splenomegaly, hepatomegaly, and lymphadenopathy. Unless steps are taken to prevent iron overload, severe haemosiderosis will develop over the span of years [3].

β-thalassaemia major manifests itself postnatally as HbF synthesis diminishes. Affected children fail to develop normally, and their growth is retarded shortly after birth. Regular blood transfusion is the mainstay of treatment in most of the developing countries which improves the anaemia and reduce the skeletal deformities associated with excessive erythropoiesis. With transfusions alone survival into second or third decade is possible, but gradually iron overload develops. Unless adequate chelation therapy is instituted haemosiderosis is an inevitable consequence of long-term transfusion therapy [1,4]. Many studies on patients with thalassaemia have demonstrated restrictive lung disease, obstructive lung disease and diffusion abnormalities [1,5-8]. But the precise cause for pulmonary function abnormalities is not clearly known. Most of the studies that correlates serum ferritin levels with PFTs have shown inconsistent results [1,2,5-9]. This shows that there is paucity of data in this regard from India. So the aim of this study was to determine the frequency of pulmonary function abnormalities in multitransfused children with β-thalassaemia major and to compare these abnormalities with normal children.

MATERIALS AND METHODS

The present study was a case-control study conducted from May 2012 to June 2013 at MS Ramaiah Medical College, Bengaluru, Karnataka, India. Institutional Ethics Committee (IEC) approval (approval no. IEC565/15) was taken for the study and written informed consent was obtained from parents of all the subjects after fully explaining the nature of the study. The study included 70 children who fulfilled the following criteria.

Inclusion criteria: Thirty five children between age group 3-16 years with confirmed diagnosis of β-thalassaemia major attending thalassaemia ward and on regular blood transfusion to maintain haemoglobin levels at or above 11 g/dL with or without iron chelation therapy [10] were included as cases. Thirty five age and sex matched normal children participated as controls.

Exclusion criteria: Children with respiratory diseases, cardiac diseases and asthma were excluded from the study.

The literature review [5,6] indicated mean FVC level to be around 79.6 (SD±15.4) among β-thalassaemia major patients as compared to 91.7 (SD±9.5) among normal subjects. In order to estimate the above differences with the power of 80% and alpha error of 5% it was estimated that nearly 35 children with β-thalassaemia major and 35 children in control group were studied.

Study Procedure

Children who fulfill the inclusion criteria for the study were selected. General demographic data like age, sex, height and weight were collected from all children. Details like age at diagnosis, age at first blood transfusion, cumulative amount of blood transfusions, duration of iron chelation therapy, age at start of chelation therapy, pretransfusion haemoglobin level, mean ferritin level over preceding one year were collected from β-thalassaemia major children. Physical examination findings were recorded on a proforma.

The PFTs were done using SMITHS MIR Spirobank G version 1.0 with BTPS 1.026 spirometer, within three days of blood transfusion in thalassaemia major children [1]. PFT was done in standing posture. Each child was given a demonstration before performing the test. They were instructed to inspire slowly as much air as possible and then expire all of the air as fast as possible. Then without removing the mouthpiece from the mouth finish the test by inspiring again as fast as possible. Following parameters were recorded in the spirometry - FVC, FEV1, FEV1/FVC, PEFR, FEF25%-75%. PFTs were done three times at the interval of 5-10 minutes, and the best values were taken for the study. The results obtained were classified as normal or restrictive or obstructive pattern based on FEV1 and FEV1/FVC values. Normal values were taken as FEV1-80%, FEV1/FVC-within 5% of predicted [11] and PEFR is 60-440 L/min [12]. Decreased FVC, decreased or normal FEV1 and FEV1/FVC >0.7 indicated restrictive lung impairment, normal or decreased FVC, decreased FEV1 and FEV1/FVC <0.7 indicated obstructive lung impairment, a reduction in FEF25-75% of <60% of that predicted may confirm the airway obstruction [11]. Serum ferritin levels were estimated by chemiluminescent immunometric assay [5]. Haemoglobin estimation was done by Beckman Coulter machine using cyanmethaemoglobin automated method.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) 17.0 statistical package was used for analysing data and testing hypotheses. Descriptive statistics- Mean, median and standard deviation were used to compare the various quantitative parameters such as FVC, FEV1, FEV1/FVC, FEF25%-75%, PEFR. Student's- test was used to compare PFT parameters between cases and controls. Probability value of <0.05 was considered as statistically significant.

RESULTS

Total 35 participants in each case and control group were studied, of which 18 were males and 17 were females. Mean age of study participants of both case and control was 9.11±3.36. General characteristics of the subjects like age, sex, height, weight were collected and tabulated in [Table/Fig-1].

Parameters	Control N (35) Mean±SD	Cases N (35) Mean±SD	p-value
Age (yrs)	9.11±3.36	9.11±3.36	-
Weight (kgs)	27.69±9.99	23.66±6.98	0.0545
Height (cms)	133.46±18.35	123.63±14.36	0.0143
Sex- Males	18	18	-
Females	17	17	-

[Table/Fig-1]: Shows the general characteristics of the subjects.
Student's-test used

Median age at start of transfusion was eight months and at start of chelation therapy was 3.6 years [Table/Fig-2]. All patients were analysed regardless of sex, and there were no significant differences between controls and cases in the PFT parameters like FVC (%predicted), FEV1 (%predicted), FEV1/FVC, PEFR (%predicted), and they were in the normal range. However the FE 25-75% was 84.34±26.77 in the control group and was within normal range whereas in children with β-thalassaemia major it was 69.34±27.06 and significantly lowered (p-value=0.023) [Table/Fig-3].

Variables	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
Pretransfusion Hb (gm%)	8.50 (6.8-11.4)	8.56±1.14	8.16-8.95	2
Cumulative amount of transfusion (mL) of blood	13650.00 (850-37200)	15018.33± 8084.17	11999.65-18037.01	9225
Serum ferritin (ng/mL) preceding one year	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/Fig-2]: Shows haematological characteristics of thalassaemia children.

PFT parameters	Control Mean±SD, n-35	Cases Mean±SD, n-35	p-value
FEV1 (%pred)	90.74±16.92	96.06±41.58	0.06
FVC (%pred)	89.37±17.57	114.43±77.30	0.486
FEV1/FVC	99.40±8.041	92.57±20.09	0.066
PEFR (%pred)	108.71±93.47	91.97±62.23	0.381
FEF (25%-75%)	84.34±26.77	69.34±27.06	0.023*

[Table/Fig-3]: Shows comparison of PFT parameters between cases and controls.
*Significant Student t-test was used for comparison

The PFTs showed that all children who were controls had normal values. Among thalassaemia major, 20 (57.14%) children were normal and 15 (42.86%) children had respiratory abnormalities among which restrictive, obstructive and mixed cases are shown in [Table/Fig-4].

Type	Cases (%)
Normal	20 (57.14)
Restrictive	9 (25.71)
Obstructive	5 (14.29)
Mixed	1 (2.86)

[Table/Fig-4]: Percentage abnormalities of pulmonary function tests in thalassaemia children (n=35).

DISCUSSION

Beta thalassaemia results from the abnormal synthesis of the β-chain haemoglobin; thus it usually starts to manifest as early as 4-6 months of prenatal life during the switch from HbF to HbA [2]. These patients are sustained only by repeated blood transfusions, which improve the anaemia and reduce the skeletal deformities associated with excessive erythropoiesis. Survival into second or third decade is possible with transfusion, but gradually iron overload develops. Unless patients are treated aggressively with iron chelators, cardiac failure from secondary haemochromatosis commonly occurs and often causes death in the second and third decade of life [3]. Hardly any respiratory symptoms are seen in patients with β-thalassaemia major despite the deposition of iron in the lungs. Most patients of β-thalassaemia major are still not on hypertransfusion regimen and/or regular chelation in India. Theoretically, the lungs are also at major risk of damage secondary to iron overload.

Very few studies have been done to investigate PFT on β-thalassaemia major patients. The studies conducted on children are even lesser in India [4,6]. The age at start of transfusion therapy (mean±SD 16.41±16.07 years) was comparable to the age of the children in many studies [4,6,8,13-15]. Pretransfusion haemoglobin (mean±SD 8.56±1.14 gm%) of this study was also comparable with other studies [2,6,8,10,13,14,16]. Cumulative amount of blood transfusion (mean±SD of 15018.33±8084.17 mL) had been used in this study as a measure of iron overload, in contrast to a study done by Sohn EY et al., [4] have calculated years of transfusion. The

serum ferritin levels in this study (mean±SD 2719.75±1909.92 ng/dL) were also comparable with other studies [5,6,13].

Lung function has been studied in patients of β-thalassaemia major using various tests. The commonest PFT done is Spirometer. FVC, FEV1, FEV/FVC, FEF (25%-75%), PEFR, Total Leukocyte Count (TLC) and Residual Volume (RV) are among the lung volumes and capacities studied. Few studies have also measured single breath diffusion capacity of the lungs for carbon monoxide (DLCO), Arterial Blood Gas (ABG) and chest X-ray (CXR), High Resolution Computer Tomography (HRCT) and Broncho Alveolar Lavage (BAL) including body plethysmography in full inspiratory and expiratory thin-section CT [1,2,5-9,10,13,17].

Slight differences have been found in the extent of pulmonary dysfunction in different studies. In this study, PFT showed that the percentage of pulmonary dysfunction was 42.86%. However the percentage of patients with abnormal pulmonary function were 62.5%, 48.5%, and 29% in the studies by Abu-Ekteish FM et al., Parakh A et al., and Arora M et al., respectively [5,6,8]. Previous studies conducted by Alaysin S et al., and Cooper DM et al., also revealed respiratory dysfunction in β-thalassaemia major children to be 86% and 70% of cases respectively [14,15]. Despite being a subject of study in the past 30 years, controversy persists regarding the nature and pathogenesis of abnormalities in pulmonary function in children with thalassaemia [6].

Most of the investigators have found restrictive abnormality in the pulmonary function and impaired DLCO [5]. In the present study, a restrictive lung pattern had been observed as the predominant lung alteration in 25.71% of children with β-thalassaemia major. These findings were consistent with most studies on major thalassaemia patients reported in the literature. In a study by Parakh A et al., [6] 50% had normal PFT, 41.16% showed impairment in the DLCO and 16.12% of thalassemic patients had restrictive pattern of lung disease. Many other studies reported a much higher figure of restrictive pattern [5,6,18]. A study done by Abu-Ekteish FM et al., [5] restrictive pattern was seen in 35% of patients and 72.7% of patients in study by Azarkeivan A et al., [18]. Recent studies done by Gadiparthi M et.al., [19] and Abd El Hakeem AA et al., [20] also reported 73.5% and 34% cases with restrictive pattern respectively. However the aetiology of restrictive disease is still unclear.

Efforts have been made to characterise the lung impairment pattern in β-thalassaemia major to establish its aetiology to date. However, conflicting reports of both obstructive and restrictive airway diseases have been found. In the present study the frequency of obstructive cases were 14.29% and combined cases were 2.86% which was in contrast to Sohn EY et al., which reported majority had small airway obstructive disorder [4]. The obstructive component can be due to the distal airway involvement [4,14]. Similar results have been obtained by Kanj N et al., and Azarkeivan A et al., [2,18].

Another study has used thin-section Computed Tomography (CT) in patients with β-thalassaemia major [21] to evaluate pulmonary function. About one quarter of patients with thalassaemia major had air trapping at thin-section CT that was consistent with small-airway disease and in particular, obstruction. There was also a negative correlation between air trapping at thin-section CT and FEF 25%-75% an indicator of small airway disease. This negative relationship between air trapping score and FEF 25%-75% has also been described in other conditions, such as asthma and bronchiolitis obliterans in which small-airway obstruction is the predominant pathologic process. High resolution inspiratory/expiratory chest CT was used by Khong PL et al., to document air trapping in small airways obstruction. Air trapping scores were correlated with FEV1, FEV1/FVC and FEF 25%-75% [21]. There were no significant differences between controls and cases in the PFT parameters like FVC (%predicted), FEV1 (%predicted), FEV1/FVC, PEFR (%predicted), and they were in the normal range. However the FEF25%-75% was (84.34±26.77) in the control group and was within normal range whereas in children with β-thalassaemia major it was significantly lowered (69.34±27.06) mostly consistent with small airway disease. Results of this study supported the findings of Sohn EY et al., Abu Ektesh FM et al., Alyasin S et al., and Khong PL et al., [4,5,14,21]. The evolution of such respiratory alterations is not clearly known. Main pulmonary function abnormality in children with thalassaemia and the cause of pulmonary dysfunction is likely to be multifactorial [7,22].

Limitation(s)

With our facilities DLCO, TLC and RV could not be measured and hence correlation of the same with iron burden/overload had not been done.

CONCLUSION(S)

In the present study functional evaluation of patients with thalassaemia major showed a significant reduction in FEF 25%-75%, an indicator of small-airway disease, which suggests air trapping. The PFT showed restrictive and obstructive component in a few thalassaemia patients. So, further studies are necessary for acquiring greater insight into the pathogenesis of lung dysfunction in thalassaemia. Establishment of a standard therapeutic approach will help the prevention of complications and improve the quality of life of thalassaemia patients in the future.

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