



PULMONARY FUNCTION TEST IN MULTITRANSFUSED CHILDREN WITH THALASSEMIA

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Abstract

INTRODUCTION:-

Thalassemia is the most common monogenetic disorder worldwide and is a common cause of chronic haemolytic anaemia. It was first described by Thomas B Colley in 1925. The disease is transmitted by autosomal recessive manner. Thalassemia is a major health problem, placing an emotional, psychological and economic burden on millions of people around the World. Recent data indicates that about 3% of the World's population is a carrier of beta thalassemia. Every year 3,00,000 to 5,00,000 children are born each year worldwide with the severe homozygous state of this disease¹.

Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. Over the past three decades, regular blood transfusions and iron chelation have dramatically improved the quality of life and thalassemia is transformed from a rapidly fatal disease to a chronic disease and is compatible with prolonged life.

The most important complication in patients with transfusion-dependent thalassemia is progressive iron accumulation secondary to transfusion of the blood (secondary hemochromatosis) and iron accumulation-induced organ damage.² The heart, liver, and pancreas are the target organs most frequently involved in which extensive iron induced injury is regularly observed at autopsy, although abnormalities of lung mechanics have been reported by almost all studies of patients with thalassemia major. The fact that iron accumulation in the lungs is known in these patients, but how this accumulation affects the lungs is still a matter of debate².

Many studies on patients with thalassemia have demonstrated restrictive lung disease, obstructive lung disease and diffusion abnormalities³⁻⁷. However, there is no consensus about the nature, restrictive or obstructive, of these defects. Indeed, substantial iron deposition in the lung has been observed on postmortem examination in some but not in other cases. In addition to abnormal lung

mechanics, patients with thalassemia major regularly exhibit a reduced pulmonary diffusing capacity, which in most instances is only partially due to lower haemoglobin concentration⁸.

The diagnosis and management of patients with pulmonary diseases have improved with introduction of pulmonary function tests. Pulmonary function tests provide objective evidence of the nature and severity of lung diseases⁹

Thus present study was conducted to describe the predominant type of lung impairment in transfusion dependent thalassemic patients and comparison with age and sex matched normal healthy school going children and effect of age, duration of blood transfusion, duration of chelation therapy and ferritin level on pulmonary function, among age group 6-16yrs in our geographical area.

MATERIALS AND METHODS:-

A cross-sectional analytical study, during January 2020, to December 2020, in children aged between 6 to 16 years with beta-thalassemia major admitted for periodic blood transfusion in thalassemia ward, at DR. S. N. Medical College, Jodhpur.

INCLUSION CRITERIA:-

All transfusion dependent thalassemic children in the age group of 6-16 yr attending thalassemia ward of Dr. S.N. Medical College, Jodhpur and having haemoglobin >9gm/dl were included in the study.

EXCLUSION CRITERIA:-

1. Thalassemic children with co-existing congenital cardiac disease ex VSD, ASD
2. Thalassemic children with co-existing respiratory disease ex. cystic fibrosis, recent acute respiratory infections or other chronic pulmonary diseases
3. Patients having congenital defects like cleft lip and palate or neuromuscular disorder as they are unable to perform spirometry manoeuvre.

Sample size:-

Based on the previous literature, data indicate that the prevalence of abnormal pulmonary function test (PFT) in children with beta-thalassemia admitted to paediatric ward is 86–95%. To estimate the prevalence of abnormal PFT in children with beta-thalassemia within 6 percentage points of the true value of 90% with 80% confidence, we require a minimum of 65 beta-thalassemia major children to be studied.

Methodology: -

Ethical clearance was obtained from the Institutional Ethics Committee. Children who fulfill the inclusion criteria for the study were selected. Informed and written consent was obtained from parents of all cases. All enrolled children were taken detailed clinical history including age at first BT, number of BT, duration of iron chelation therapy, and general physical examination findings which were recorded on a predesigned proforma. Before BT, for all enrolled children, blood sample was sent for serum ferritin level. Serum ferritin level was measured by electrochemiluminescence technique. PFT was done using spirometer Helios 702 spirometer. Standard procedure for PFT was carried out to all enrolled children and Before testing, the procedure was explained and demonstrated to each child until full familiarity was achieved then checked test for acceptability and reproducibility.²⁵The following parameters were recorded in the spirometry – forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV1), ratio of FEV1/FVC, peak expiratory flow rate (PEFR), and forced expiratory flow between 25 and 75% vital capacity (FEF 25–75%). Interpretation of PFT was done according to the recommended guidelines by National Asthma Education and Prevention Program guidelines.¹⁰

Statistical Analysis:

A pre-structured pre-tested proforma was used for Data collection and for data analysis Microsoft excel was used. SPSS statistical software (version 21) was used for the analysis and values were

reported as mean $\pm$ SD (for values following a normal distribution). The degree of association between all variables studied was analyzed using Pearson coefficient of correlation. The combined effect of several variables on the severity of restriction was analyzed using multiple regression analysis. Summary data were presented using correlation coefficients. Results were considered statistically significant if $p < 0.05$.

RESULTS:

Total number of children included in the study was 65. Forty-two (64.62%) children were <12 years and 23 children (35.38%) were more than 12 years, with mean age 11.20 ± 2.79 and male:female ratio 1.03:1.

All children (100%) presented with easy fatigability and progressive pallor. None of the children presented with rapid breathing, chest in drawing, and chest pain. On per abdomen examination, all children had hepatomegaly (100%) and 60 children (92.30%) had splenomegaly, remaining 5 (7.70%) children were splenectomised.

Total number of children with abnormal PFTs was 30 (46.15%). Among 30 children with pulmonary dysfunction, 17 (56.66%) children had restrictive pattern, 11 (36.66%) children had obstructive pattern, and 2 (6.66%) children had combined pattern. [Table 1] shows mean values of various parameters of PFT.

Pulmonary test	Cases [n=65]
FVC (% Pred)	92.69 $\pm$ 30.88
FEV1 (% Pred)	85.81 $\pm$ 25.35
FEV1/FVC	88.55 $\pm$ 18.23
PEFR (% Pred)	92.96 $\pm$ 63.98
FEF25-75%	68.80 $\pm$ 25.25

[Tables 2] show risk factors for pulmonary dysfunction. Mean serum ferritin levels in children with Mild, Moderate and Severe pattern were 2086.87 $\pm$ 504.44, 3545.46 $\pm$ 1690.30 and 4525.57 $\pm$ 2877.00 respectively.

Restrictive pattern (FEV1%)	Serum Ferritin (ng/ml) Mean $\pm$ SD
Mild (70-80%)	2086.87 $\pm$ 504.44
Moderate (60-69%)	3545.46 $\pm$ 1690.30
Severe ($<60\%$)	4525.57 $\pm$ 2877.00

DISCUSSION:-

Lung dysfunction is among the least studied complication in children with beta-thalassemia major, probably due to the lack of pulmonary symptoms presenting compared to cardiomyopathy or endocrine complication. We observed that 30 (46.15%) children had abnormal PFT. Impairment in respiratory function among thalassemia children has been reported in the range of 29–86%.[11-13] Restrictive lung function abnormality was observed as major pulmonary abnormality in our study. Several other studies[12-16] have shown similar restrictive pattern as major pulmonary dysfunction. However, none of them found exact etiopathogenesis. We analyzed various risk factors for abnormal lung function including age, height, BMI, number of BT, duration of chelation therapy, organomegaly, and serum ferritin. Of these, age, number of blood transfusion, duration of chelation therapy and serum ferritin were significantly associated with pulmonary dysfunction (FVC%, FEV1,

and PEFR). The severity of restrictive abnormalities of thalassemic children was found to increase with age. In many other studies, different etiopathogenetic mechanisms for the development of restrictive lung dysfunction were reported such as hypoxia,[17] iron overload,[15-16] drug like desferrioximine,[17] and genetic structure.[17]

Eleven children (36.66%) had obstructive type of lung dysfunction. Similar results were found in study by Gulhan et al.[18].

We also observed the combined pattern in 2 children (6.66%). The probable reason for small number of cases could be due to limitations in screening.

It is noteworthy that none of the patients examined in the present series showed any clinical symptoms of pulmonary dysfunction. Thalassemia patients do not complain of ventilatory limitations. Thus the clinical significance of pulmonary disease in Thalassemia Major remains unclear. In the present study functional evaluation of patients with thalassemia major showed a significant reduction in FEV1, FEV1/FVC, and FEF25%-75%. Reduction in these parameters is an indicator of obstructive and small-airway disease, which suggests air trapping. The PFT also showed restrictive component in few Thalassemic patients. Hence in our study several pathological mechanisms for the pulmonary dysfunction in thalassemia can be put forward including iron overload, duration of blood transfusion, presence or absence of chelation. Chronic iron deposition in organs and tissues, as hemosiderin or free iron, might be the main factor promoting the production of free radical mediators of the oxidative damage that would enhance the onset of complications, as in our study we observed that severity of disease increased with increasing level of serum ferritin. We also observed that serum ferritin level >2500 ng/dl was associated with more reduction in PFT parameters in comparison with patients who had serum ferritin level <2500 ng/dl. Our study suggests that with improved access to iron chelation to keep serum ferritin level low and regular blood transfusion, will help in the prevention of complications and improve the quality of life of thalassemic patients .

CONCLUSION:- Majority of our thalassemia children (78%) had abnormal patterns of lung function even though none of these children had any respiratory symptoms. We suggest, all children with thalassemia on regular BT should undergo PFT annually to prevent the sequelae.

Declaration of patient consent:- The Institutional Review Board permission obtained for the study.

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