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Clinical, Hematological Profile and Status of Iron Overload in Children with Transfusion Dependent Thalassemia : A Study from Rural Northern India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Thalassemias are one of most common type of haemolytic anaemia caused due to ineffective erythropoiesis requiring lifelong blood transfusions leading to chronic iron overload resulting in vasrious complications restricting the life span of most patients to 3rd-4th decade.
Objective: To evaluate clinical, haematological profile and status of iron overload in patients of transfusion dependent thalassemia.
Methods: We have enrolled 42 patients presenting to our centre for regular blood transfusion, the participants were followed up for a period of 1 year and samples were send at 3 monthly interval for CBC, Serum ferritin(S.F) , Serum Iron(S.I) and TIBC.
Results: The most frequent presenting complaints was pallor, incidence of malnourishment was 45.2%,the mean haemoglobin at time of presentation was 6.8± 2.9 g/dl, the mean S.F(ng/ml) and S.I(mcg/dl) at commencement of study was 2059.45 ± 2082.92 and 248.99 ± 92.95 while these values increased to 2610.57 ± 2245.64 and 349.05 ± 110 respectively after 1 year follow-up. All patients received chelation therapy either in form of Deferasirox (mean S.F=1639 ± 962 mean S.I=274.5 ± 76.7) or a combination of Deferasirox and Deferiprone (mean S.F= 5350 ± 3349.7 mean S.I=397.9 ± 128.2).

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Conclusion: Majority of participants are inadequately transfused and chelation therapy was not effective in preventing iron overload which mandates a need of better and more effective chelators, revision of transfusion guidelines as well as proper counselling regarding attitude and behaviour of caregivers.

Keywords: Thalassemia; blood transfusion; iron overload; chelation therapy; deferasirox.

1. INTRODUCTION

Thalassemia is an inherited disorder due to defect in genes that help to control synthesis of haemoglobin leading to ineffective erythropoiesis. It is estimated that every year about 100,000 children are born worldwide with transfusion dependent thalassemia, out of these 8000-10000 are reported in India alone [1].These patients require life-long blood transfusions which results in chronic iron overload causing various complications like growth retardation, delayed sexual development in period of adolescence, various organ dysfunctions including heart, liver, kidneys, pancreas and other endocrine glands [2]. However the only curative option is hematopoietic stem cell transplantation which is still offered at very few centres in India.

Since there are no mechanisms in the human body to excrete extra iron, patients who require regular transfusion therapy are at risk of developing chronic iron overload. Chelation therapy, in addition to transfusion therapy, is an important part of the clinical management of these patients. The optimal time for initiation of chelation therapy has not been defined, but it should not be delayed in order to prevent the manifestations of iron overload in various organs of the body. It should be started when: (a) Serum ferritin approaches 1000 ng/dl (b) Patient has received 15-20 transfusions (c) Hepatic iron concentration exceeds 3.2 mg/g dry weight [3].

Of the three iron chelators available, Deferoxamine is administered by a subcutaneous infusion pump while other two Deferiprone and Deferasirox are administered by oral route. Deferasirox is available as a dispersible tablet given at a dose of 20-40 mg/kg empty stomach with mild adverse effects like rashes, Deferiprone is given at a dose of 75 mg/kg under supervision due to development of adverse effects like arthritis, neutropenia and agranulocytosis. Combination therapy may be needed in children not adequately controlled on a single chelator [4]. Different clinical parameters are used to assess body iron burden and response to therapy which includes serum ferritin levels (most commonly used), liver biopsy and cardiac MRI. Sustained ferritin levels greater than 1000 mcg/l are associated with organ toxicity and death and is targeted to be <2500mg/L by use of chelators [5].

In our study we have studied clinical, biochemical, haematological profile and iron overload status of children presenting to our centre with transfusion dependent ß-Thalassemia over a period of 1 year.

2. MATERIALS AND METHODS

This prospective cohort study was conducted on children with age group 1-15 years presenting in Dept. of Pediatrics, UPUMS, Etawah(U.P) over a period of 1 year after taking due approval from Institutional Ethical Committee. A written and well informed consent was taken from parents of children after explaining them nature of study, enrolment was free from any kind of biases. Children with age <1years or >15years, having unstable vitals at time of admission, on injectable chelation therapy and guardians refusal to give consent were excluded from study. On the basis of inclusion criteria, 42 patients were enrolled in the trial and were followed up on every three months for a year, with samples sent for Complete Blood Count (CBC), General Blood Picture (GBP), Serum Ferritin(SF), Serum Iron, and Total Iron Binding Capacity (TIBC). Serum ferritin was measured by DRG® Ferritin ELISA (EIA-4292) kits, serum iron was measured with help of Hewlett Packard 8452A diode array spectrophotometer. Treatment in form of blood transfusion , chelation therapy in form of deferasirox or deferasirox plus deferiprone were given in all patients while symptomatic treatment were given accordingly. The data was analysed using Microsoft excel and SSPS 22.0.

2.1 Sample Size

A total 42 patients fulfilling inclusion criteria were included in our study and followed up over a period of 1 year every 3 monthly.

3. OBSERVATION AND RESULTS

We have included total 42 patients in our study in which 33 (78.5%) are males and 9 (21.5%) are females. We have divided our study group according to age into 3 groups i.e. 1-5years, 5-10 years and 10-15 years. The most common presenting complaint was progressive pallor which was present in all 42 patients at the time of presentation. Fever was present in 7 patients at presentation and was most frequent in age group 1-5 years (16.6%). Jaundice was present in 17 patients at time of presentation (7, 7 and 3 patients in age groups 1-5 years, 5-10 years and 10-15 years respectively). On examination liver span was found to be normal in only 2 children in the age group 1-5 years while rest of patients had enlarged liver span according to age. Massive splenomegaly was present in 10 patients (4, 3 and 3 patients in age groups 1-5 years, 5-10 years and 10-15 years respectively) and moderate splenomegaly was present in 18 patients (7, 10 and 1 patients in age groups 1-5 years, 5-10 years and 10-15 years respectively). Head size was found enlarged in total 14 patients (6, 3 and 5 patients in age groups 1-5 years, 5-10 years and 10-15 years respectively) while the rest 28 patients had normal head size. Thalassemic facies was present in 21 out of 42 patients (9, 11 and 1 patients in age groups 1-5 years, 5-10 years and 10-15 years respectively). Out of 42 patients, 19 patients were found to be malnourished (8, 8 and 3 patients in age groups 1-5 years, 5-10 years and 10-15 years respectively) and 4 patients have incomplete immunisation.

We have further classified patients into 3 groups according to level of haemoglobin at time of presentation during 1st, 2nd, 3rd and 4th visits i.e. <5mg/dl, 5-7mg/dl and >7mg/dl. Most of the patients presented when the haemoglobin was 5-7mg/dl, only 4, 6, 3, 3 patients presented with haemoglobin >7mg/dl during the 1st, 2nd, 3rd and 4th visits respectively (Table-2). The mean haemoglobin at time of presentation was 6.8± 2.9 g/dl.

Table 1. Clinical and epidemiological profile of thalassemic patients

		1-5 years	5-10 years	10-15 years
Sex	Male	15	12	6
	Female	1	8	0
Pallor	Present	16	20	6
	Absent	0	0	0
Fever	Present	3	3	1
	Absent	13	17	5
Jaundice	Present	7	7	3
	Absent	11	13	3
Liver Span	Enlarged	14	20	6
	Normal	2	0	0
Liver Span	<3cm	5	7	2
	3-7cm	7	10	1
	>7cm	4	3	3
Head Size	Normal	10	17	1
	Enlarged	6	3	5
Thalassemic Facies	Present	9	11	1
	Absent	8	9	5
Malnourishment	Present	8	8	3
	Absent	9	12	3
Immunization	Complete	13	19	6
	Incomplete	3	1	0
Education of Father	Illiterate	2	5	0
	Primary	5	3	3
	High-School	4	5	3
	Graduation	5	7	0
Education of Mother	Illiterate	5	2	4
	Primary	3	6	0
	High-School	7	8	2
	Graduate	1	4	0

Table 2. Haemoglobin at presentation during 3-monthly visits

Haemoglobin at Presentation(g/dl)	1st visit	2nd visit	3rd visit	4th visit
<5mg/dl	3	4	5	2
5-7mg/dl	35	32	34	37
>7mg/dl	4	6	3	3

Table 3. Haematological parameters during 3-monthly visits

		1st visit	2nd visit	3rd visit	4th visit
S. Iron (mcg/dl)	Mean	248.99	279.70	314.40	349.05
	SD	92.95	94.55	101.3	110.85
	Minimum	125.70	150.20	176.20	195.50
	Maximum	567.70	608.40	698.30	796.60
S. Ferritin (ng/ml)	Mean	2059.45	2294.40	2419.31	2610.57
	SD	2082.92	2259.15	2221.02	2245.64
	Minimum	215	320	450	600
	Maximum	10000	12000	11900	12200
TIBC (mcg/dl)	Mean	155.47	148.80	142.40	136.07
	SD	20.21	18.01	16.35	15.46
	Minimum	110	106	100	92.70
	Maximum	198.40	190.60	186.60	180.80

Table 4. Comparison of haematological parameters of iron overload in patients receiving Deferasirox vs combination of deferasirox and deferiprone

	Deferasirox		Deferasirox+Deferiprone	
	Mean	SD	Mean	SD
Serum Iron (mcg/dl)	274.5	76.7	397.9	128.2
Serum Ferritin (ng/ml)	1639	962	5350	3349.7
TIBC (mcg/dl)	148.2	16.7	134.7	17.4

Iron overload status of the patients was determined by measurement of serum iron, serum ferritin and total iron binding capacity every 3 monthly (Table-3). The mean serum iron(mcg/dl) during 1st visit was 248.99 ± 92.95 which increased to 349.05 ± 110.85 after 1 year while mean serum ferritin(ng/ml) during 1st visit was 2059.45 ± 2082.92 which increased to 2610.57 ± 2245.64 in the duration of 1 year.

Out of 42 patients enrolled in our study 8 patients were taking a combination of deferasirox and deferiprone as chelation therapy, while the remaining 34 patients were taking only deferasirox as chelation therapy. The mean and standard deviation values of serum iron, ferritin and TIBC were calculated over a period of 1 year, it is evident that these values are higher in the group receiving both chelators and there is statistically significant difference in both the groups (p-value <0.05).

4. DISSCUSSION

Thalassaemia is prevalent worldwide but it is more prevalent in certain geographical areas and communities. Due to various advancements and availability of better health care facilities the average life span of transfusion dependent ß-Thalassemia patients have increased to 3rd-4th decade of life. Optimal management of transfusion dependent Thalassaemia is challenging as under transfusion will lead to growth retardation, pallor, jaundice, poor

musculature, hepatosplenomegaly, leg ulcers, and development of masses from extramedullary haematopoiesis and skeletal changes that result from expansion of the bone marrow while regular blood transfusion will lead to chronic iron overload resulting in endocrine complication (growth retardation, diabetes mellitus, insufficiency of the parathyroid, thyroid, pituitary, failure of sexual maturation and less commonly, adrenal glands), dilated cardiomyopathy, liver fibrosis and cirrhosis. Thus management requires a multidisciplinary team of haematologists, paediatrician, surgeons as well as especially trained nurses and supporting staff. Management since childhood and effectiveness of chelation therapy have major impact on outcome of disease in relation to frequency and severity of complications. In present study we have studied clinical, epidemiological and haematological parameters of 42 patients over a period of 1 year.

In our study the male to female ratio of participants was 3.6:1 which was different from 2.3:1 [6], 1.5:1 [7] and 1.37:1 [8], this difference may be explained by neglect of girl child as well as difference in genetics in geographical areas. Incidence of malnutrition was 45.2% in our study which was similar to 48.2% [9] and 41.8% [10] as reported in previous studies, reaffirming the fact that thalassemics are at higher risk for malnourishment and growth failure. The mean haemoglobin at the time of presentation was 6.8± 2.9 g/dl which was more or less similar to that reported previously in various studies 6.25 ± 1.6 g/dl [11] and 6.09 ± 1.61 g/dl [12], it denotes lack of awareness in caregivers about the ill effects of Thalassaemia on growth and development of child and importance of maintenance of normal haemoglobin as the average duration of blood transfusion was 45 days in our study. The incidence of pallor, fever, jaundice, thalassemic facies was 100%, 16.7%, 40.5% and 50% respectively which was similar as reported in previous studies [12,13,14] except for pallor which have a higher incidence in our study. The mean serum ferritin at 1st visit was 2059.45 ± 2082.92 ng/ml while mean serum ferritin after 1 year follow up was 2610.57 ± 2245.64 ng/ml, similarly serum iron(mcg/dl) values were 248.99 ± 92.95 and 349.05 ± 110.85 during 1st visit and after 1 year follow up respectively. These values were comparable to previous studies in which average serum ferritin values were 2597.2 ± 1976.8 ng/ml [15], 2698 ± 1444 ng/mL [16], 2341.98 ng/ml [17] while some studies have reported higher levels of ferritin and serum iron levels [18]. These findings denote that despite oral chelation therapy it is difficult to prevent development of iron overload states leading to development of complications. In our study there is significant iron overload in the form of serum iron with significant value($p<.001$) with significant decrease in correction of TIBC is also highly significant($p<.001$) which signify that despite of oral iron chelator, a constant amount of iron is deposited in the body that can not be affected by oral iron chelator so there is a consistent increase in serum iron along with consistently reduced values of TIBC. In our study all patients were taking some form of oral chelation therapy since start of study, out of 42 participants 34 were taking oral deferasirox which is provided by government free of cost while rest 8 were taking a combination of deferasirox and deferiprone. Deferiprone was added in treatment regimen after persistence of very high levels of serum ferritin despite adequate therapy with deferasirox and unavailability of desferrioxamine at our centre. The mean serum ferritin, serum iron and TIBC of patients receiving deferasirox was determined to be 1639 ± 962, 274.5 ± 76.7, 148.2 ± 16.7 respectively while the values for the group receiving combination of deferasirox and deferiprone was 5350 ± 3349.7, 397.9 ± 128.2, 134.7 ± 17.4 respectively, these values were significantly higher than normal values indicating a chronic iron overload in patients of transfusion dependent thalassemias.

5. CONCLUSION

As evidenced by the high incidence of malnutrition, low mean haemoglobin at presentation, and high mean serum ferritin and iron, in our study we can conclude that the majority of subjects are insufficiently transfused with inadequate chelation therapy. These findings point to the need for stronger and more effective chelators, revised transfusion standards, and suitable counselling for caregivers attitudes and behaviour. More longitudinal research are needed, however, to have a deeper understanding of these findings.

STRENGTHS

1- Inclusion and exclusion criteria are well defined and strictly adhered while recruiting the cases.
2- We attempted to find factors that have effect on final outcome hence efforts for improved survival of thalassemia major patients can be taken.

3- Chelation therapy was provided free of cost to the participants thus minimising economic burden on participants in a developing country like India.

LIMITATIONS

1- 1-Our study is a single centre study involving limited number of participants with a followup period of 1 year, a longer period of follow up of patients is required for better understanding of morbidity , clinical complications and deaths.
2- Non availability of injectable chelators
3- Iron overload cant be assessed appositely due to non availability of cardiac MRI for assessment of cardiac iron overload, liver biopsy for liver iron studies and hormonal assays to assess endocrinological complications.
4- Duration of oral iron chelation wasnt considered.

FUTURE PROSPECTS

1- Newer drugs like PIH (pyridoxal isonicotynoyl hydrozone) HBED- and dimethyl HBED for chelation are promising as they are relatively non toxic and effective.
2- Pharmacological manipulation of HbF inducing drugs like hydroxyl urea, butyrates, 5-azacytidine54. Pharmacological gene manipulations heve been tried in order to increase the production of HbF and to prevent the precipitation of unpaired Hb chains.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

A written and well informed consent was taken from parents of children after explaining them nature of study, enrolment was free from any kind of biases.

ETHICAL APPROVAL

This prospective cohort study was conducted on children with age group 1-15 years presenting in Dept. of Pediatrics, UPUMS, Etawah(U.P) over a period of 1 year after taking due approval from Institutional Ethical Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Thiyagarajan A, Bhattacharya S, Sharma N, Srivastava A, Dhar DK. Need for a universal thalassemia screening programme in India? A public health perspective. J Family Med Prim Care 2019;8:1528-32
2. Gao C, Li L, Chen B, Song H, Cheng J, Zhang X, Sun Y. Clinical outcomes of transfusion-associated iron overload in patients with refractory chronic anemia. Patient preference and adherence. 2014; 8:513.
3. Marwaha RK, Lal A: Present status of hemoglobinopathies inIndia: Indian Pediatrics, 1994;3:267-71.
4. Kolnagou A, Kontoghiorghes GJ. Chelation protocols for the elimination and prevention of iron overload in thalassaemia. Front Biosci (Landmark Ed). 2018;23:1082-1098.
5. Mobarra N, Shanaki M, Ehteram H, Nasiri H, Sahmani M, Saeidi M, Goudarzi M, Pourkarim H, Azad M. A review on iron chelators in treatment of iron overload syndromes. International Journal of Hematology-Oncology and Stem Cell Research. 2016;10(4):239.
6. Simhachalam M, Sahoo M, Kuppili U. A study on growth profiles in children with thalassemia major between 2-10 years of age on regular transfusions and oral chelation therapy. Int J Pediatr Res. 2018; 5(2):78-86.
DOI: 10.17511/ijpr.2018.2.07
7. George A, Bhaduri A ,Sen S ,Choudhry VP. Physical growth parameters in thalassemic children. Indian J Pediatr. 1997;64:861–871
8. Pemde HK, Chandra J, Gupta D, Singh V, Sharma R, Dutta AK. Physical growth in children with transfusion-dependent thalassemia. Pediatric Health, Medicine and Therapeutics. 2011;2:13-9.

9. Biswas B, Naskar NN, Basu K, Dasgupta A, Basu R, Paul B. Malnutrition, its attributes, and impact on quality of life: an epidemiological study among β-thalassemia Major Children. Korean journal of family medicine. 2021;42(1):66.
10. Fuchs GJ, Tienboon P, Linpisarn S, Nimsakul S, Leelapat P, Tovanabutra S, Tubtong V, DeWier M, Suskind RM. Nutritional factors and thalassaemia major. Archives of disease in childhood. 1996; 74(3):224-7.
11. Phadke SR, Agarwal S. Phenotype score to grade the severity of thalassemia intermedia. The Indian Journal of Pediatrics. 2003;70(6):477-81.
12. Shah R, Trehan A, Das R, Marwaha RK. Serum ferritin in thalassemia intermedia. Indian Journal of Hematology and Blood Transfusion. 2014;30(4):281-5.
13. Kumar S, Singh D, Garg A. An epidemiological study on the clinico-hematological profile of pediatric patients with congenital hemolytic anemia. Int. J. Contemp. Pediat. 2017;4:374-7.
14. Ali MR, Bari MI, Mia MS, Rahman MK, Hossain MF, Sharmin LS. Clinical Profile of Thalassemia Syndrome in Children of Northern Bangladesh. TAJ: Journal of Teachers Association. 2018;31(2):6-11.
15. Belhoul KM, Bakir ML, Saned MS, Kadhim AM, Musallam KM, Taher AT. Serum ferritin levels and endocrinopathy in medically treated patients with β thalassemia major. Annals of hematology. 2012;91(7):1107-14.
16. Shalitin S, Carmi D, Weintrob N, Phillip M, Miskin H, Kornreich L, Zilber R, Yaniv I, Tamary H. Serum ferritin level as a predictor of impaired growth and puberty in thalassemia major patients. European journal of haematology. 2005;74(2):93-100.
17. Taneja R, Malik P, Sharma M, Agarwal MC. Multiple transfused thalassemia major: ocular manifestations in a hospital-based population. Indian journal of ophthalmology. 2010;58(2):125.
18. Chandra J, Chaudhary H, Pemde H, Singh V, Dutta AK. Safety and efficacy of deferasirox in multitransfused Indian children with β-thalassaemia major. Ann Trop Paediatr 2011;31:47-51

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