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Study The Effect Of Combination Iron Chelation Therapy In Transfusion Dependent B Thalassemia Major

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Abstract

Background and aims: Due to the availability of safe blood transfusions even at the village and district levels lead to the increased survival in transfusion dependent thalassemic children but at the same time it has leads increase iron overload and its complication in these patients. Deferasirox is the most commonly used iron chelation agent but in many children it is not able to decrease S. ferritin level to desired level hence require addition of other drug.

Material and method:A prospective analytical study was carried out to assess the effect of combination iron chelation therapy on children with transfusion-dependent beta thalassemia major children age between 6-18 years of age who are on Deferasiroxmonotherapy and S.ferritin>2500 ng/dl. All patients who were enrolled in the study were started on combination iron chelation therapy with Deferiprone at a dose of 75 -100 mg/kg was added with Deferasirox after baseline investigations like S.Ferritin and growth parameters like Height, weight and Sexual maturity rating (SMR) were done every 3 monthly and asked for regular follow up for blood transfusion.

Results –Statistically significant lower mean serum ferritin values were observed when the combination iron chelation therapy was used as compared to deferasiroxmonotherapy with p value 0.0022(p value<0.05) . There is no statistically significant difference in the height,weight and pubertal parameters were observed at the end of the study.

Conclusion- Combination iron chelation therapy with deferasirox and deferiprone is more effective than monotherapy with deferasirox for reducing serum ferritin level in children with β thalassemia major in age between 6-18 years with serum ferritin >2500 ng/ml with deferasiroxdose > 36mg/kg/day. Combination iron chelation therapy is relatively safer with minimal transient side effect.

Keywords: Deferasirox, Deferiprone,Beta thalassemia major

Introduction

Thalassemia is an autosomal recessive hemolytic genetic disorder due to imbalance between alpha and beta globin chain production resulting in an ineffective synthesis in hemoglobin chains[1]. The mainstay of therapy of thalassemia major consists of repeated and regular red cell concentrate (RCC) transfusion from early childhood to correct the anemia and reduces the morbidities associated withanemia and excessive erythropoiesis[2]. Multiple repeated blood transfusions becomes the key intervention in managing such children due to the availability of safe blood transfusions even at the village and district levels lead to the increased survival in transfusion dependent thalassemic children but at the same time it has leads increase iron overload and its complication in these patients[3]. To overcome this we have to start iron chealtion therapy once patients had received 10-12 transfusions or whose ferritin>1000ng/L.Deferasirox is the most commonly used iron chelation agent, as it is raltively safe and orally available . Despite of good compliance and maximum dose of Deferasirox many of the children have ferritin level in thousands which in turn lead to complication and deterioration in quality of life; in such patients it require addition of another iron chelating agent[4,5]. As the data regarding the combination iron chelation therapy in Indian setting is limited, hence we hadplan an analytical study to study the effect of the combination iron chelation therapy in trasnfusiondepenedent thalassemia major to prevent and reduce complications related to iron overload[6].

Material and methods:

A prospective analytical study was carried out to assess the effect of combination iron chelation therapy on children with transfusion-dependent beta thalassemia major at Civil Hospital, Ahmedabad. Children who are diagnosed with beta thalssemia major based on hemoglobin electrophoresis, whose age between 6 years to 18 years and who are taking regular blood transfusion at our hospital and who are on iron chelation mono therapy (Deferasirox) and whose S.ferritin>2500 ng/dl were enrolled after written informed consent for a period 1/7/21 to 31/12/23. Children who are <6 years and >18 years, children who are diagnosed with beta thalassemia major or intermedia who are transfusion independent[1], children with beta thalassemia major but taking blood transfusion from other hospitals, children who are on iron chelation therapy but not on Deferasirox or taking combination iron chelation therapy from other hospitals were excluded from the study. Institutional committee

approval was taken before the initiation of the study. The patients and their relatives were explained about the study protocol and after which a written informed consent was taken at the time of enrolment. After the enrolment in the study basic demographic features like age, sex, religion, caste, religion and address with contact number were recorded in a pre-designedproforma. Patients presenting complaints at the time of enrolment, age of diagnosis of beta thalassemia major, age at which first blood transfusion was started, age at which iron chelation therapy initiated, detailed history of blood transfusions taken so far and detailed history of chelation therapy from initiation to the enrolment date and other significant history, detailed past history, family history, birth history, developmental history, immunization history were also recorded in the pre designed proforma. At the time of enrolment baseline anthropometric parameters like height, weight, Sexual maturity rating staging(in the age group of >8 years), general examination and systemic findings were also recorded. Baseline investigations like Complete blood count, S.ferritin level, Renal function test, Thyroid function test, serological testing for HIV, HBSAg, HCV, Ophthalmological evaluation, 2D echo were also done at the time of enrollment and their reports also recorded in the proforma. After the enrollment in the study population along with Deferasirox at the dose of >/= 36mg /kg day, Deferiprone was started at the dose of 75 mg/kg/day in three divided doses daily. Children were asked to take Deferasirox in the morning with water, and also Tablet Deferiprone at the dose of 75 mg/kg/day 3 times after each major meals with water. After initiation of dual drug therapy if patient's S.ferritin level remains same or increase level of S. ferritin than dose of Deferiprone was increased by 10 mg/kg/day every 3 monthly till a maximum dose of 100 mg/kg/day. The enrolled children were followed every monthly at centre and at each visit their complaints and compliance of the drugs were checked and the dosage of the drugs were explained and counselled about the drug intake and parameters like BMI, Height, weight, and S. Ferritin level assessed every 3 monthly and HIV, HBsAg and HCV serology were done every 6 monthly till up to 12 months post enrolment period and its findings were recorded. At each visit compliance and side effects of the therapy were also assessed[6]. Children who failed to come for the follow up were excluded from the study. At the completion of study data was summarized in form of tables and conclusions drawn by appropriate statistical tests by using appropriate statistical software.

Results

During the enrolment period 40 patients of beta thalassemia major who were on regular blood transfusion therapy[1]& fulfilling the inclusion criteria were included in the study and the following observations were made from the present study. Out of 40 enrolled children 22 were male and 18 were female with male to female ratio is 1.2:1. 16 children were between 6-9 years of age,11 children were between 10-13 years of age and 13 children between 14-18 years of age. Mean age of enrolment was 11.7±3.7 years. 85% children were Hindu by religion and 15% children were muslim by religion. Rajput, Prajapati, Brahmin and Harijan are the common castes observed in study population. 24(60%) children had positivefamily (sibling) history of thalassemia minor and 3(7.5%) children had history of consanguineous marriage[2]. Most common symptoms at the enrolment of these patients were pallor (100%), followed by not gaining weight (35%) and fever (25%),Abdominal pain (25%), Fatigue/weakness (20%) and abdominal distension (17.5%) were other common symptoms observed. In the present study out of 40 children 28(70%) children were had hepatomegaly, 25(62.5%) children had splenomegaly and 3(7.5%) children were have signs of cardiac iron overload in form of Pulmonary artery hypertension and arrhythmia at the initiation of combination therapy[3].

There is statistically significant decrease in serum ferritin levels were observed at 3 months,6 months and 12 months after initiating combination therapy as compared to deferasiroxmonotherapy with chi square value 25.69 and p value 0.0022.(p value<0.05) . In the present study the optimum mean dose requires for decrease mean serum ferritin level of was deferiprone92.8±10.3 mg/kg/day and deferasirox was 40.1±2.9 mg/kg/day of deferasirox. No statistically significant difference observed in height, weight, pubertal parameters and organomegalyparameters with 12 months of combination iron chelation therapy.In present study the most common side effect observed during combination therapy was GI disturbances in 16(40%), neutropenia in 5(12.5%), raised transaminases levels in 5(12.5%), arthropathy which in 1(2.5%) and recurrent stomatitis seen in 1(2.5%) children[4,5]. For these complaints deferiprone was stopped for temporary in 9 patients and in 2 patients due to right knee joint arthropathy in 1 patient and recurrent stomatitis in 1 patient.

Parameter (n=40)	Observations from the current study
Number of male children	22(55%)
Number of female children	18(45%)
Male to female ratio	1.2:1
Mean age of study population	11.7±3.7 years

Mean age of enrollment	6-9 years	
Mean age at which blood transfusion started	7.7±5 months	
Mean age of diagnosis	10.3±4.6months	
Mean age at which iron chelation therapy started	3.5±2 year	
Distribution according to religion		
Muslim	6 (15%)	
Hindu	34 (85%)	
Distribution according to caste		
Rajput	8(20%)	
Brahmin	5(12.5%)	
Prajapati	5(12.5%)	
Harijans	3(7.5%)	
History of consanguineous marriage present	3 (7.5%)	
Childrenwith positive family(sibling) history	24(60%)	
Seroprevalence of transfusion transmitted infections	HIV	0
	Hepatitis B	0
	Hepatitis C	3(7.5%)

Quarterly serum ferritin levels of the patients during the combination iron chelation Therapy with Deferasirox and Deferiprone.

Ferritin(ng/ml)	No. Of patients (n=40)				P value	Chisquare
	Baseline	3 months	6 months	12 months		
<2500	0	4	7	7	0.0022	25.69
2500-5000	19	27	27	20		
5000-7500	17	6	4	10		
>7500	4	3	2	3		

Deferasirox+deferiprone as a chelator agent: by the relative change in serum ferritin levels measured.

Dose of deferasirox	Dose of deferiprone	Change in serum ferritin levels		
		Decrease	Increase	Total(N=40)
>36 mg/kg/day(1)	70-80mg/kg/day(4)	3	1	4
>36 mg/kg/day	80-90mg/kg/day(4)	3	1	4
>36mg/kg/day	90-100mg/kg/day(23)	18	4(1 NO CHANGE)	23
>36mg/kg/day	>100mg/kg/day(9)	9	0	9

Effect of combination iron chelation therapy on Growth, organomegaly and cardiac iron overload

Parameter	**Before starting chelation therapy (n=40)**	**After starting chelation therapy (n=40)**	**P value**
Under nutriton (Total =40)	11(27.5%)	7(17.5%)	0.11
Short stature (Total =40)	14(35%)	11(27.5%)	0.10
Delayed puberty(N=24)			
Male-12(30%)	2(5%)	2(5%)	0.1 t(2)

Female-12(30%)	6(15%)	4(10%)	
Hepatomegaly	28(70%)	13(32.5%)	0.092
Splenomegaly	25(62.5%)	13(32.5%)	
Signs of cardiac iron overload			
PAH	2(5%)	0	0.09
ARRHYTHMIA	1(2.5%)	0	
NORMAL	37	40	

Discussion

These were the observations made from 40 patients of beta thalassemia major[1] who were on regular blood transfusion therapy with age between 6-18 years who are on monotherapy with deferasirox with dosage >36mg/kg/day and whose serum ferritin level >2500ng/ml and following are observation of the study.Out of 40 enrolled children 22 were male and 18 were female with male to female ratio is 1.2:1. Male predominace (Male to Female ratio 1.5:1) was also observed in mutlicentric study which was done by Bhatia et al involving 4 major cities of India[7]. In present study 16 children were between 6-9 years of age,11 children were between 10-13 years of age and 13 children between 14-18 years of age with Mean age of enrolment was 11.7±3.7 years in present study.Mean age of enrollment in Totadri et al study was 13±6.9 years which was on 36 patients with thalassemia major conducted at chandigarh[8].

13(32.5%) children had received first blood transfusion before the age of 6 months out of only 2 were diagnosed as thalassemia major before the age of 6 months and 11 children were diagnosed after the age of 6 months, as these children belonging to the remote area where diagnostic facilities were not available hence diagnosis was delayed. Mean age at diagnosis of thalassemia major was 10.3±4.6months.In a study conducted by Trehan et al at PGIMER Chandigarh 44.2% children had received first bloodtransfusion in age between 6-12 months with mean age of first blood transfusion was 9.9±6.4 months and mean age of diagnosis was 13.2±9.7 months[8].

In thepresent study 34(85%) children were Hindu by religion and 6(15%) children were Muslim by religion. Rajput, Prajapati, Brahmin and Harijan are the common castes observed in the present study because, these were the dominant castes prevalent in the area were Civil hospital Ahmedabad located. In the study by Trehan et al 61% children were Hindu by religion, 35% were Muslim by religion and 6% were belonging to other religion. The common caste observed in Trehan et al study wereKhatri, Arora, Baniya and Rajput[8].

In present study most common symptoms were pallor (100%), followed by not gaining weight (35%) and fever (25%). Abdominal pain (25%), Fatigue/weakness (20%) and abdominal distension (17.5%) were other common symptoms observed in present study at the time of enrolment[11].In present study none of the child had infection with HIV, Hepatitis B virus and Hepatitis C Virus at the initiation of study. Only 3(7.5%) children were infected with hepatitis C virus infection only during study period. This is due to Nucleic Acid amplification test (NAAT) is use by our blood bank for screening of these diseases.

There were 17 children in whom monotherapy with tablet deferasirox has been started before the age of 3 years and 23 children in whom monotherapy started after the age of 3 years. Mean serum ferritin value at the initiation of combination therapy observed were 4961.9±904.4 ng/ml and 5753.7±1217.8 ng/ml respectively in both these groups. There was statistically significant lower mean serum ferritin value observed in children in whom deferasirox started before the age of 3 years as compared to children in whom deferasirox started after the age of 3 years ($P < 0.05$).

In the current study mean serum ferritin level at the initiation of combination therapy was 5317±1366.6 ng/ml and after 12 months of combination therapy mean serum ferritin level was 4368.4±2158.2 ng/ml with statistically significant decrease in mean serum ferritin level was observed at 12 months. The subjects with initial serum ferritin level of >7500 ng/ml had an inadequate response to combination therapy. There is statistically significant decrease in serum ferritin level was observed at 3 months,6 months and 12 months after initiating deferasirox+deferiprone combination therapy as compared to deferasiroxmonotherapy(p 0.0022).There is statistically significant decrease in mean serum ferritin level was observed at 12 months after initiatingdeferasirox+deferiprone combination therapy as compare to deferasiroxmonotherapy with p value 0.008(p value<0.05). Optimum mean dose requires for decrease mean serum ferritin level is 92.8±10.3

mg/kg/day of deferiprone and 40.1±2.9mg/kg/day of deferasirox. While in a similar study by Totadri et al mean dose of deferiprone was 84.4±5.2 mg/kg/day and deferasirox was 33.4±5.2 mg/kg/day[8].

In present study out of 40 children 14(35%) children were have short stature at the initiation of combination therapy and at the end of 12 months of combination therapy out of 40 children 11(27.5%) children were having short stature (height <3rd centile). In present study out of 40 children 11(27.5%) children were have underweight at the initiation of combination therapy and at the end of 12 months of combination therapy out of 40 children 7(17.5%) children were having underweight. In the present study out of 40 enrolled children 24(60%) children were more than 10 years of age in whom 6 monthly SMR staging was done. Out of these 24(60%) children 12(30%) children were male and 12(30%) children were female. Out of these 24(60%) children 8(20%) were had delayed puberty at the initiation of study and all of them had delayed puberty at the end of 12 months of therapy. In present study there is no statistically significant difference observed in growth-height, weight parameters and pubertal parameters with 12 months of combination iron chelation therapy according to paired t test (p value 0.1, 0.11 ,and0.1 respectively). Long term of follow up is required to study the effect of combination therapy on height, weight and pubertal parameters.

In the present study out of 40 children 28(70%) children were have hepatomegaly and 25(62.5%) children were having splenomegaly. There is no statistically significant effect of combination therapy onorganomegaly was observed in the present study (p value 0.092). Out of 40 enrolled children 3 children had signs of cardiac iron overload at the initiation of combination therapy; these were Pulmonary artery hypertension in two child (10 & 18 years old) and one had arrhythmia age (15 year).After 12 months of combination therapy none of enrolled child had signs of cardiac iron overload on 2D echo cardiography.

In present study the most common side effect observed during combination therapy was GI disturbances in 16(40%) childrenfollowed by neutropeniain 5(12.5%) children.Other observed side effects were raised transaminases level in 5(12.5%) children, arthropathywhich in 1(2.5%) and recurrent stomatitis seen in 1(2.5%) child.In Alan R et al study 33.2% children had side effects in form of GI disturbances, 8.5% children had neutropenia, 28% children had raised transaminases level and 15% children had arthropathy[9].In Gomber et al study 13.3% children had side effects in form of GI disturbances and 6.6% child had arthropathy[10].In present study out of 40 enrolled children 11(27.5%) children required discontinuation of deferiprone due to its side effect. Out of 11 children 9(22.5%) children had transient side effects in form of GI disturbance and neutropenia. Symptoms of these children were improved with 1-2 weeks of discontinuation of therapy and deferiprone was restarted in these patients.In present study out of 11(27.5%) children who required discontinuation of deferipronepermanently as 1(2.5%) developed right knee joint arthropathy after 10 months of initiation of combination therapy and 1 having recurrent stomatitis after 7 months of combination therapy .

Conclusion

Combination iron chelation therapy with deferasirox and deferiprone is more effective than monotherapy with deferasirox for reducing serum ferritin level in children with β thalassemia major age between 6-18 years with serum ferritin >2500 ng/ml with deferasirox dose > 36 mg/kg/day.Combination iron chelation therapy is relatively safer with minimal transient side effect.Optimum dose of deferiprone for combination iron chelation therapy is 90- 100 mg/kg/day.

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