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COMPARATIVE EFFICACY OF DIFFERENT ORAL IRON CHELATORS IN MULTIPLY TRANSFUSED THALASSAEMIA PATIENTS

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ABSTRACT

Background: Thalassaemia is not that uncommon disease and it has lots of morbidities and mortalities. Repeated Blood Transfusions at regular intervals, still remains as the treatment of choice due to very many reasons, leading eventually, to iron over loading and its complications. The management of iron overload in these patients requires the administration of iron chelators continuously and evaluation of serum ferritin levels at regular intervals. This study was undertaken in the Department of Pediatrics, S.C.B. Medical College & SVP PGIP, Cuttack, in collaboration with the Department of Clinical Hematology, S.C.B. Medical College, Cuttack, Odisha during the period from January, 2012 to June, 2013 with an aim and objective to compare the efficacy of different oral iron chelators for clinical use. **Materials And Methods:** The study included 60 patients of Thalassaemia, out of which 50 were β-thalassaemia major and 10 β-Thalassaemia intermedia. Study population (after fulfilling inclusion and exclusion criteria) was divided into two Treatment Groups a) Deferiprone and b) Deferasirox, each consisting of 30 patients chosen randomly, for giving the drug. After detailed history and physical examination, all were investigated, given chilators and re-investigated after 6 months of chelation therapy. During statistical analysis one group acted as the control for the other group. **Results:** The study included 60 patients of Thalassaemia, out of which 50 were β-thalassaemia major and the rest 10 were β-Thalassaemia intermedia. Treatment Groups a) Deferiprone and b) Deferasirox, each consisted of 30 patients. Out of 60 patients, 42(70%) had significant (≥ 15%) decrease in serum ferritin level, but the decrease was more marked in Deferasirox group (41.7%) than Deferiprone group (28.3%). **Conclusion:** Even though both Deferiprone and Deferasirox are effective at decreasing iron burden, from the point views of several characteristics, Deferasirox is favoured over Deferiprone.

KEYWORDS: Thalassaemia, Iron Chelators, Multiply Transfused, Ferritin, BT.

INTRODUCTION

The thalassaemias are a heterogenous group of disorders with a genetically determined reduction in the rate of synthesis of one or more types of normal haemoglobin polypeptide chain, which results in a decrease in amount of haemoglobin involving the affected chain thus being described as the quantitative disorders in which, the primary lesion lies for globin produced. The only way of treating these thalassaemic children and preventing the complications due to severe anemia is by repeated blood transfusions at regular intervals, which is again, not free from its ill effect.

An inevitable, important and potentially lethal complication of administering repeated blood transfusions to a child with thalassaemia is a gradual overloading of the body with Iron (Heinrich *et al*, 1973).[1] Unchecked transfusional siderosis produces syndrome closely similar to that of idiopathic hemochromatosis and this leads remorselessly to death usually towards the end of the second decade, the immediate cause being as a rule, cardiac failure. Whether adequately or inadequately transfused, iron overload is inevitable in thalassaemia major. Establishment of more favourable iron balance should lead to improved survival; this belief has motivated detailed study of several iron-unloading maneuvers. The management of iron overload in these patients requires the administration of iron chelators continuously and evaluation of serum ferritin levels at regular intervals. In this group of chelators, first to be introduced into clinical practice was Desferrioxamine. But due to cumbersome route of administration, hospital stay & other significant challenges associated with its use lead to non-complaince. Next to this were Deferiprone and Deferasirox, oral iron chelators became easily available and evidence supports their use in chronic iron over load. They have many side effects like growth retardation, cataract, hematological abnormalities (agranulocytosis), endocrinological abnormalities etc. In some regions like

Europe they only approve deferiprone but other regions like USA only approve deferasirox. But in a developing country like India both are available freely. So in this context iron chelators must be used rationally and balanced in relation to the benefit to the patient and toxicity profile. There is paucity of studies co-relating effectivenes of different oral iron chelators over the other in multiply transfused thalassaemia children, in our region.

AIMS AND OBJECTIVES

Aim: To compare the efficacy of different oral iron chelators for clinical use.

Objectives: a) Primary objective: To compare the decrease in S. Ferritin levels between two study groups, one under deferiprone and other with deferasirox. b) Secondary objective: i) To study the adverse effect profile due the treatment in study groups. ii) To study the change in biochemical and hematological parameters in study group due to treatment.

MATERIALS AND METHODS

This randomized case-control study was undertaken in the Department of Pediatrics, S.C.B. Medical College & SVP PGIP, Cuttack, in collaboration with the Department of Clinical Hematology, S.C.B. Medical College, Cuttack, Odisha. Investigations were done in the Department of Pathology, Biochemistry and Central laboratory of S.C.B. Medical College, Cuttack during the period from January, 2012 to June, 2013. All the patients, who were diagnosed as β-thalassaemia major or intermedia presenting to out-patient department or admitted to the indoor wards of Pediatrics or Clinical Hematology Department of S.C.B. Medical College, Cuttack, full filling the inclusion criteria, were examined & investigated in detail as per pre prepaired proforma.

Inclusion Criteria: a) Children ≤14 years of age, b) Diagnosed cases of β-thalassaemia major / intermedia on haemoglobin electrophoresis or HPLC, c) History of receiving multiple blood transfusions (≥10) at apparently regular intervals, d) Serum ferritin level (≥1000 µg/L) and e) Patient's care taker who had given consent for the study.

Exclusion Criteria: a) Moribund patients or patients with life threatening complications, b) Thalassaemia minor, c) Hemodynamically unstable patients, d) Irregularly transfused patients and e) Cases not strictly adhered to the treatment protocol prepared for the individuals. Sixty children below the age 14 years full-filling inclusion criteria comprised the materials for the study in present series. After detailed and focused history and physical examination, patients were subjected to base-line hematological investigations like Hb%, DC, TLC, PCV, ESR, Reticulocyte count, CPS, absolute neutrophil count, RFT (S.Urea, S.Creatinine), LFT (AST, ALT, ALP, S.Billirubin) along with S.FERRITIN (Study variable).The suitable patients were choosen for administration of oral iron chelators. Thirty patients were given Deferiprone at a dose of 75 mg/kg in three divided doses. Another half were given Deferasirox at 30 mg/kg once daily empty stomach with half glass of juice or water. The patients were chosen randomly for allocation of drugs. Cases were strictly instructed to follow the treatment plans prepared for the individual child. Each patient was followed up monthly for a minimum period of six months. At each follow up, base line hematological investigations along with the required test were done. Increase of serum urea and creatinine 25% above the base line were considered significant. Elevation of liver enzymes (AST ALT), S. Billirubin twice the base line value during follow up were considered significant. Neutrophil count $<1.5\times10^9$/L were taken as neutropenia and $<0.5\times10^9$/L were considered as agranulocytosis. At the end of six month, patients were again subjected to S. ferritin level and the data collected during the study were analysed statistically to compare the clinical parameters and biochemical parameters, Chi-square test of association has ben used. For comparison of the study variable (S. Ferritin), Independent student t-test has been used. For comparison of number of BT with S. ferritin, Pearson's correlation coefficient has been used. The analysis has been done using SPSS-13 software.

RESULTS

The study included 60 patients of Thalassaemia, out of which 50 were β-thalassaemia major and the rest 10 were β-Thalassaemia intermedia. (Table-1) Study population was divided into two Treatment Groups a) Deferiprone and b) Deferasirox, each consisting of 30 patients chosen randomly, for giving the drug. Age-wise, 40%, 35% and 25% children patients in the study population belonged to the age groups 1-5 yrs, 6-9 yrs. and 10-14 yrs respectively. Male patients out-numbered the Females (57% vs 43%).

Pallor (97%) was the commonest finding encountered followed by Hepato-slenomegaly (82%), Mongoloid facies and Growth retardation (70% each), Odema (37%), Isolated splenomegaly (18%) and only 7% had clinical jaundice at presentation.(Table-2) Eighty percent of children under study group had maintained their hemoglobin level more than 7 gm% at their presentation. (Table-3). During the treatment period, a total of 4 patients had increase in Serum urea and Serum creatinine 25% above their base line values, out of which 1 (3.3%) patient belonged to Deferiprone group and other 3 (6.7%) to Deferasirox group (Table-4). Treatment group on Deferasirox had increased incidence of G.I. symptoms (36.7%) and rash (13.3%). Only 1 patient (3.3%) had arthropathy. The group receiving Deferiprone had 33.3% incidence of G.I. symptoms, 16.7% had arthropathy and related disorder and only 3.3% incidence of rash and agranulocytosis. (Table-5). There was a significant and linear correlation between the age and number of Blood Transfusion with that of rise in Serum ferritin. (Table-6 and Table-7).

The mean ferritin in deferiprone and deferasirox groups were 1829.6±704.7 and 1838.8±720.9 respectively, at the start of chelation therapy. After six-month use of chelation, the mean ferritin levels in deferiprone and deferasirox cohort were 1603.7±666.2 and 1313.3±631.7 respectively (Table-8).

Out of 60 patients, 42(70%) had significant (≥ 15%) decrease in serum ferritin level, out of which 25 (41.7%) and 17(28.3%) belonged to Deferasirox and Deferiprone cohorts respectively. The mean decrease in ferritin level with Deferiprone cohort was 225.9±188.1 and with Deferasirox cohort was 525.5±400.1. With p-value of 0.00004, it clearly suggested that decrease in ferritin level with Deferasirox was much better than that with Deferiprone (Table-9).

Table-1: Distribution of Study Subjects by Category: β-Thalassaemia major/intermedia (N=60)

Category	Treatment Groups				Total		Chi Square & p Value
	Deferiprone		Deferasirox				
	Number	%	Number	%	Number	%	
β- Thalassaemia Major	25	83.33	25	83.33	50	83.33	0.0004
β-Thalassaemia Intermedia	5	16.67	5	16.67	10	16.67	1.000
Total	30	100	30	100	60	100	

Table-2: Distribution of Study Subject by Physiological Characteristics (N=60)

Physiological Characteristics		Treatment Groups				Total		Chi Sqaure & p Value
		Deferiprone		Deferasirox				
		Number	%	Number	%	Number	%	
Pallor	Yes	30	100	28	93.33	58	96.67	2.069
	No	0	0	2	6.67	2	3.33	0.150
	Total	30	100	30	100	60	100	
Jaundice	Yes	2	6.67	2	6.67	4	6.67	0.000
	No	28	93.33	28	93.33	56	93.33	1.000
	Total	30	100	30	100	60	100	
Edema	Yes	12	40	10	33.33	22	36.67	0.287
	No	18	60	20	66.67	38	63.33	0.592
	Total	30	100	30	100	60	100	
Mongoloid Facies	Yes	22	73.33	20	66.67	42	70	0.317
	No	8	26.67	10	33.33	18	30	0.573
	Total	30	100	30	100	60	100	
Hepato Splenomegaly	Yes	24	80	25	83.33	49	81.67	0.111
	No	6	20	5	16.67	11	18.33	0.739
	Total	30	100	30	100	60	100	
Isolated Splenomegaly	Yes	6	20	5	16.67	11	18.33	0.111
	No	24	80	25	83.33	49	81.67	0.739
	Total	30	100	30	100	60	100	
Growth Retardation	Yes	22	73.33	20	66.67	42	70	0.317
	No	8	26.67	10	33.33	18	30	0.573
	Total	30	100	30	100	60	100	

Table-3: Distribution of Study Subject by initial Hb% level (N=60)

Initial Hb% level	Treatment				Total		Chi Sqaure & p- Value
	Deferiprone		Deferasirox				
	Number	%	Number	%	Number	%	
<7 mg/dl	7	23.33	5	16.67	12	20	
7 - 9 mg/dl	13	43.33	19	63.33	32	53.33	2.458
≥ 9 mg/ dl	10	33.33	6	20	16	26.67	0.293
Total	30	100	30	100	60	100	

Table-4: Association between Bio-chemical Parameter and Treatment (N=60)

		Treatment Groups				Total		Chi Square & p Value	Contingency Coefficient & p Value
		Deferiprone		Deferasirox					
		Number	%	Number	%	Number	%		
Increased S. Urea	Yes	1	3.33	3	10	4	6.67	1.071	0.132
	No	29	96.67	27	90	56	93.33	0.301	0.301

	Total	30	100	30	100	60	100		
Increased S. Creatinine	Yes	1	3.33	3	10	4	6.67	1.071 0.301	0.132 0.301
	No	29	96.67	27	90	56	93.33		
	Total	30	100	30	100	60	100		
Increased S. Bilirubin	Yes	1	3.33	0	0	1	1.67	1.017 0.313	0.129 0.313
	No	29	96.67	30	100	59	98.33		
	Total	30	100	30	100	60	100		
Increased AST	Yes	1	3.33	2	6.67	3	5	0.351 0.554	0.076 0.554
	No	29	96.67	28	93.33	57	95		
	Total	30	100	30	100	60	100		
Increased ALT	Yes	1	3.33	2	6.67	3	5	0.351 0.554	0.076 0.554
	No	29	96.67	28	93.33	57	95		
	Total	30	100	30	100	60	100		

Table-5: Association of Adverse Effect and Treatment (N=60)

		Treatment Groups				Total		Chi Square & p Value	Contingency Coefficient & p Value
		Deferiprone		Deferasirox					
		Number	%	Number	%	Number	%		
Agranulocytosis	Yes	1	3.33	0	0	1	1.67	1.017 0.313	0.129 0.313
	No	29	96.67	30	100	59	98.33		
	Total	30	100	30	100	60	100		
G I Symptoms	Yes	10	33.33	11	36.67	21	35	0.073 0.787	0.035 0.787
	No	20	66.67	19	63.33	39	65		
	Total	30	100	30	100	60	100		
Rash	Yes	1	3.33	4	13.33	5	8.33	1.964 0.161	0.178 0.161
	No	29	96.67	26	86.67	55	91.67		
	Total	30	100	30	100	60	100		
Arthopathy/ Arthritis	Yes	5	16.67	1	3.33	6	10	2.963 0.085	0.217 0.085
	No	25	83.33	29	96.67	54	90		
	Total	30	100	30	100	60	100		

Table-6: Correlation between Age and S. Ferritin (N=60)

		S. Ferrrtin Zero Month	S. Ferritin Six Month
Age (In Yr)	Pearson Correlation Coefficient	0.736(**)	0.669(**)
	P-Value	0.0001	0.0001
	N	60	60
**Correlation is significant at the 0.01 level (2-tailed). p<0.01			

Table-7: Correlation between Serum Ferritin and No. of BT (N=60)

		S. Ferritin Zero Month	S. Ferritin Six Month	S. Ferritin Difference
No of Units of BT	Pearson Correlation Coefficient	0.76**	0.66**	0.28*
	p-value	0.001	0.001	0.03
	N	60.00	60.00	60.00
** Correlation is significant at the 0.01 level (2-tailed) P<0.01 * Correlation is significant at the 0.05 level (2-tailed) P<0.05				

Table-8: Comparison of Ferritin Level between Treatment Group (N=60)

Time	Treatment Group	Statistic				
		Mean Ferritin	95% Confidence Interval for Mean		Std. Deviation	t & p
			Lower Bound	Upper Bound		
Zero Month	Deferiprone	1829.6	1566.5	2092.7	704.7	t= 0.50 p=0.960
	Deferasirox	1838.8	1569.6	2108	720.9	
Six Month	Deferiprone	1603.7	1355	1852.5	666.2	t= 1.732 p=.088
	Deferasirox	1313.3	1077.4	1549.2	631.7	

Difference	Deferiprone	225.9	155.6	296.1	188.1	t= 3.7115
	Deferasirox	525.5	376.1	674.9	400.1	p=.00004

Table-9: Decrease in Ferritin level Vs Treatment Group (N=60)

Decrease in Ferritin	Treatment Groups				Total	
	Deferiprone		Deferasirox			
	Number	%	Number	%	Number	%
Ferritin Decrease ≥15%	17	56.67	25	83.33	42	70
Ferritin Decrease <15%	8	26.67	1	3.33	9	15
Ferritin Increase	5	16.67	4	13.33	9	15
Total	30	100	30	100	60	100

DISCUSSION

Out of 60 patients of thalassaemia, 50 were β-thalassaemia major and the rest 10 were β-thalassaemia intermedia. There is a male predominance of thalassaemia (M: F = 57%:43%). Pallor (97%) was the commonest finding that was encountered, next to that 82%, patients had combined hepato-slenomegaly, 70% patients had mongoloid facies & growth retardation. 37% patients had edema & 18% had isolated splenomegaly at presentation. Only 4 patients, i.e 7% had clinical jaundice at presentation. All presenting features correlating well with that found by Baty J.M. *et al.* in 1932.[2] All these clinical features were also described by Cooley & Lee (1925); Whipple & Bradford (1936).[3,4]

Maximum number of patients (80%) maintained their hemoglobin level above 7 gm%. But this data can be misguiding as population were highly selective and that included only a small number of patients. During the treatment & observation period, 4 patients had increase in S. Urea & S. Creatinine 25% above their base line values. Out of which 1 (3.3%) patient belonged to Deferiprone group & other 3 (6.7%) to Deferasirox group.

During this period 1(3.3%) patient of deferiprone group had increase in Serum bilirubin, AST & ALT twice their base line values but 2 (6.7%) patients of other group had the same without any effect on S. Bilirubin. Elevations of liver transaminases have been reported during deferiprone treatment. An early trial suggested that deferiprone was associated with progressive liver fibrosis, (Olivieri NF *et al.* 1998).[5] This was a small trial involving 19 patients of which 5 were considered to have progression of liver fibrosis. Subsequent trials involving larger numbers of patients have not demonstrated liver toxicity. (Wanless A *et al.* 2002 and Tondury P*et al.* 1998).[6,7] Liver enzyme elevations tend to be mild and reversible. In a recent pediatric trial 12% of patients experienced a mild elevation in ALT. Only 1 patient had an elevation greater than twice the upper limit of normal at 3 and 6 months. Deferiprone was continued in all patients without incident.

In deferasirox, most concerning adverse effect is acute renal insufficiency. This has been reported in up to 1/3 of patients in trials. (Cappellini MD *et al.* 2006, Cappellini MD *et al.* 2010 and Piga A *et al.* 2006).[8,9,10] Generally the elevations are mild and transient, however up to 10% of patients can have an increase greater than 33% above baseline. (Cappellini MD *et al.* 2010).[9] These abnormalities almost always resolve following drug discontinuation. The variation detected in our study may be due to smaller population group & lack of further follow up for prolonged period.

Among the two groups, those receiving deferasirox had more incidence of G.I symptoms, i.e (36.7%) & rash (13.3%). Only 1 patient (3.3%) had arthropathy. The group recieving deferiprone had 33.3% incidence of G.I symptoms, 16.7% had arthropathy and related disorder & only 3.3% incidence of rash and agranulocytosis. Similar results were observed by Hoffbrand AV *et al.* 2003 and Piga A *et al.* 2010.[11,12] Neutropenia is typically reversible upon discontinuation of the drug, but can reoccur if deferiprone is reintroduced. Gastrointestinal symptoms such as nausea, vomiting and abdominal pain have been reported in up to 33% of patients. Arthralgias and arthritis have been associated with deferiprone. Although it has been reported to occur in 30-40% of patients in some studies, large trials have reported a much lower incidence of 4%. (Ceci A *et al.* 2002).[13]

Deferasirox is generally well tolerated and the adverse effects associated being mild and self-limiting which seems to be idiosyncratic and not dose dependent. (Taher A *et al.* 2009).[14] Gastrointestinal symptoms, such as nausea, vomiting and abdominal pain, as common and have been reported in upto 1/3rd of patients. (Cappellini MD *et al.* 2008, Pennell DJ *et al*, 2010 and Cappellini MD *et al.* 2010).[9,15,16] There is a significant and linear correlation between the age and number of B.T. with rise in serum ferritin. As per Model and Berdoukas in 1984[17], each unit of transfused red cells contain 200-250 mg of iron i.e. each ml of blood contain 0.5 mg of iron. So, the present study data correlates well with past data. The mean ferritin in deferiprone group (1829.6±704.7) and deferasirox group (1838.8±720.9) at the starting of Chelation therapy are quite comparable with studies by Zachariah M *et al* in 2013.[18] After six month of chelation therapy, the mean ferritin levels in deferiprone and deferasirox cohort were 1603.7±666.2 and 1313.3±631.7 respectively. Even though the ferritin levels are close to significant levels, the mean decrease in ferritin level with deferasirox cohort (525.5±400.1) was much better than that of deferiprone cohort

(225.9±188.1). This observation is quite comparable with the results of Algren D.A. *et al*. 2010.[19]

Although both DEFERASIROX and DEFERIPRONE decrease the iron overload, from above study observations (Table-10) and discussions, it appears from viewpoints of single dosing schedule, better compliance, minor self-limiting side effects that, DEFERASIROX may be a better oral iron chelator in comparison to DEFERIPRONE for clinical use.

Table-10: Comparative properties of DEFERASIROX and DEFERIPRONE

PROPERTY	DEFERASIROX	DEFERIPRONE
Chelator: Iron binding	2:1	3:1
Route of administration	Oral	Oral
Usual dosage	30 mg/kg/day	75mg/kg/day
Schedule	Once daily	Three times/day
Common Adverse effects	G.I. symptoms, rash & alteration in renal parameters	G.I. symptoms, arthropathy, agranulocytosis
Advantage & Disadvantage	Single dosing better compliance	Multiple dosing & poor compliance
Cost of therapy	Costlier than deferiprone	Comparatively cheaper than deferasirox.

SUMMARY AND CONCLUSION

The study included 60 patients of Thalassaemia, out of which 50 were β-thalassaemia major and the rest 10 were β-Thalassaemia intermedia and the Study population was divided into two Treatment Groups a) Deferiprone and b) Deferasirox, each consisting of 30 patients chosen randomly. Age-wise, 40%, 35% and 25% children patients in the study population belonged to the age groups 1-5 yrs, 6-9 yrs. and 10-14 yrs. Respectively and Male patients out-numbered the Females (57% vs 43%). Pallor (97%) was the commonest finding encountered followed by Hepato-slenomegaly (82%), Mongoloid facies and Growth retardation (70% each), Odema (37%), Isolated splenomegaly (18%) and only 7% had clinical jaundice at presentation. Most of the patients (80%) maintained their hemoglobin level more than 7 gm % at their presentation.

During the treatment period, a total of 4 patients had increase in Serum urea and Serum creatinine 25% above their base line values, out of which 1 (3.3%) patient belonged to Deferiprone group and other 3 (6.7%) to Deferasirox group.

Treatment group on Deferasirox had increased incidence of G.I. symptoms (36.7%) and rash (13.3%). Only 1 patient (3.3%) had arthropathy. The group receiving Deferiprone had 33.3% incidence of G.I. symptoms, 16.7% had arthropathy and related disorder and only 3.3% incidence of rash and agranulocytosis.

There was a significant and linear correlation between the age and number of Blood Transfusion with that of rise in Serum ferritin. The mean ferritin in deferiprone and deferasirox groups were 1829.6±704.7 and 1838.8±720.9 respectively, at the start of chelation therapy. After six-month use of chelation, the mean ferritin levels in deferiprone and deferasirox cohort were 1603.7±666.2 and 1313.3±631.7 respectively.

Out of 60 patients, 42(70%) had significant (≥ 15%) decrease in serum ferritin level, but the decrease was more marked in Deferasirox group (25(41.7%) than Deferipronegroup (17(28.3%).

Thalassaemia is not that uncommon disease and it has lots of morbidities and mortalities. Repeated Blood Transfusions at regular intervals, still remains as the treatment of choice due to very many reasons, leading eventually, to iron over loading and its complications. Even though both Deferiprone and Deferasirox are effective at decreasing iron burden, from the point views of several characteristics like once daily dosing requirement, relative ease of administration, better impact on the lowering serum ferritin, requirement of less frequent blood count monitoring and treatment adherence, Deferasirox is favoured. Although more research and long-term follow up studies are needed in pediatric age group for both oral chelators, it is proposed that deferasirox be considered the oral chelator of choice in pediatric patients with transfusion-associated chronic iron overload in thalassaemia patients.

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