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EFFICACY OF ONCE A MONTH SINGLE DOSE INTRAVENOUS (DEFEROXAMINE) VERSUS DAILY ORAL (DEFERASIROX) IRON CHELATOR IN THALASSEMIA MAJOR: AN OPEN LABEL RANDOMIZED PARALLEL GROUP ACTIVE CONTROL INTERVENTIONAL TRIAL

Pediatrics

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ABSTRACT

Objective: Compare efficacy of Once a Month Single Dose Intravenous (Deferoxamine) with Daily Oral (Deferasirox) Iron Chelator in Thalassemia Major.
***Methodology*:** In this open label trials Patients were randomized by chit method after informed consent and allocated to two groups. Group A was administered Inj Deferoxamine by intravenous route once during monthly blood transfusions and Group B received Tab Deferasirox administered daily. The monitoring was done by serum Ferritin level every two months.
Results: The primary outcome was decrease in ferritin level over 6 months from the baseline. Decrease in serum ferritin (%) over six months for Group A was 46±18 and Group B was 25±17 with *significant* difference between the two groups (p=0.001). The cost of treatment per kilo weight was not *significantly* different.
Conclusion: We observed that Intravenous Deferoxamine once a month is a better and cheaper iron chelator as compared to the daily subcutaneous regimen;

KEYWORDS

Introduction:
Thalassemia is a genetic disorder of globin chain production resulting in an imbalance between alpha and beta chain production. [1]

Signs of β Thalassemia are anemia, Thalassemia facies, hepatomegaly, and spleenomegaly. Treatment for Thalassemia major involves regular blood transfusions and definitive treatment is bone marrow transplant. Multiple transfusions cause iron build up that is stored as pigment Hemosiderin and ferritin in skin, heart, liver, spleen and endocrine organs. Accumulation of iron toxins causes tissue damage, heart failure, diabetes, hyperthyroidism, lung failure, cirrhosis, etc , hence patients require chelation therapy to reduce the iron burden added with each transfusion and prevent its long term consequences mentioned above. Criteria to start iron chelators is s. ferritin >1000 ng/ml. Dosing Regimen starts from 20-40 mg /kg/dose with maximum dose 60 mg/kg/dose.

Chelation is a chemical process in which a compound is administered to remove heavy metals or minerals from body.

There are three iron chelators available; two are oral (tablets Deferasirox and Deferiprone) and the other is injectable (Deferoxamine).

There are total 65 patients of Thalassemia major taking regular transfusion from our department at tertiary care centre. On studying the s. ferritin level of Thalassemia major patients with growth failure or those with increasing yearly blood transfusion requirement; we found that, some patients on oral iron chelator had, complains regarding compliance for daily dosing, irregular monitoring of s. ferritin and resultant inadequate dose titration, and plateau effect in s. ferritin after maximum dose (60 mg/kg/day) of oral chelator was achieved so there was a need for inj Deferoxamine or oral Deferiprone.

Injectable iron chelator Deferoxamine is administered subcutaneously 5/7 days a week by a pump. Subcutaneous pump costs 40000 Indian rupees and majority of parents were unable to understand how to operate the pump, the other alternative was to give it by infusion pump in hospital set up though it required new intravenous canulation and still the 5-7 days/ week was practically impossible as many patients were from the peripheries of Bhavnagar. In Thalassemia patients due to thrombosis intravenous canulation was also a difficult task and painful to the patient as well because of the multiple attempts/ puncture in thrombosed veins

So a study was designed to assess the effectiveness of intravenous injectable form administered with a novel dosing schedule of once a month when the child was admitted for regular blood transfusions, reducing an additional puncture for intravenous canulation.

Material and Methods:
After getting clearance from the *IRB* and *Clinical Trial Registry of India (CTRI)* registration (*ctri.nic.in CTRI/2017/08/009441*); a prospective comparative efficacy open label trial was conducted at Pediatric department of Government Medical College.

Informed written Consent was taken from parents; after explaining the study, its purpose, duration, and side effects of drugs. Once selected; they were randomized by chit method into two groups.

Total 65 Thalassemia major patients were registered in pediatric ward, out of which 14 patients were not fitting into the inclusion criteria (β Thalassemia major patients from 3 to 18 years, s. ferritin more than 1000 mg/dl, with positive consent for study).

and 18 were excluded as per the exclusion criteria; Age < 3years or > 18 years, Renal failure, Cataract, Ototoxicity, HIV positive, Hepatitis B / C positive, AV block, Asthma, Ongoing infection, history of Severe allergy) and one was removed after side effects of iv (chest tightness); remainder 32 patients were continued for trial. All these patients were followed up for six months and monitored by two monthly s. ferritin level; their base line s. ferritin was noted [flowchart *fig 1*].

Group A (16) was administered Intravenous Deferoxamine once a month and Group B (16) was administered daily Tablet Deferasirox. Intravenous injection was prepared in normal saline; if the diluted drug was milky it was discarded, if the solution was clear it was administered over seven hours, as a single dose; 1.5 hour after blood transfusion. Even if patient received second blood transfusion next day, or any time before 30 days, the drug was not repeated.

It was administered in 50 cc syringe ranging from 20-40 mg /kg/dose as per the ferritin levels. Patients with ferritin >10000 ng/ml received dose of 40 mg/kg, patients with ferritin from 7000 to 10000 ng/ml received dose of 30 mg/kg, patients with ferritin 5000 to 7000 ng/ml received dose of 20 mg/kg; maximum dose received was 40 mg/kg and once a month only. Average weight was 34 kg; average dose in 16 patients was 30 mg/kg/dose once a month.

In Group B Tablet Deferasirox was administered every day on empty stomach with lemon water or fresh orange juice and feeds were allowed 1.5 hour after drug ingestion. In patients with serum ferritin 1000 to3000 ng/ml, a dose 20 mg/kg/day was administered; with 3001 to 5000, 30 mg/kg/day and more than 5000 ng/ml a dose of 40 mg/kg/day was administered. Patients were monitored for any side effects.

The main outcome of the study was inferred in the form of serum ferritin which was done by chemiluminesence method; baseline level and then every 2 month for 6 months (total 4 samples). The changes in their level from baseline over six months were studied.

Statistics:

For statistics a software namely Graph Pad instat3 was used. Statistical analysis was done by Anova test, two tailed unpaired t test and one tailed unpaired t test.

Results

The age and sex of both groups were comparable as there was no statistically significant difference. The main outcome was decrease in serum ferritin over 6 months from the baseline level [*table 1*]. Group A (n=16) with Mean± SD at base 10850.12± 3846.5 and 5508 ±1969 at 6 months [*fig 2*] and of Group B (n=16) with Mean± SD at base 6750± 2536.4 and 3853.75± 2095.6 at 6 months [*fig 3*] with high significance (p=0.001). Decrease in serum ferritin in % over 6 months with Mean(%) ± SD of Group A is 46.16± 18.26 and Group B is 24.76± 16.84 [*fig 4*]. There is significant difference in the decrease of serum ferritin level in both the groups (p=0.001) but the % decrease is more in patients of group A than Group B.

Total cost of drugs of Group A was 25,092 and that of Group B was 193,680 and cost per kg of all pts in Group A was 53 and of Group B was 478. Cost of 500 mg tablet was 43 and 250 mg tablet was 26; injection cost was 123. Cost of group A once monthly intravenous was 4182 and that of group B daily tablets was 32280; (difference is significant p=0.001) [*table 2*]. There was less decrease in complaint of breathlessness probably due to less decrease in iron load from cardiac tissue.

No side effects were observed in our study in both groups, except one who developed chest tightness after 1 minute of starting intravenous Deferoxamine and was excluded due to such side effects (*table 3*).

Discussion:

Comparison with other studies is as per *table 3*. Injectable route, intravenous, was selected over intramuscular and subcutaneous route as it has more compliance and no additional puncture was done for drug administration as it was given from the same intravenous catheter after blood transfusion, this is similar to the results of Olivier's study *who observed that* Deferoxamine administered through implantable venous access ports reduce the local pain and irritation of subcutaneous infusions, and are associated with rapid reduction of body iron burden. [2]

The iron chelator in our study was given iv once a month after blood transfusion as compared to the study by Valymara, where administered dose was 40-50 mg/kg/day by subcutaneous route over 8-12 hours 4-6 days/week. [3]

Symptoms due to iron toxicity: though there was significant decrease in serum ferritin level from its basal reading, there was less decrease in complaint of breathlessness probably due to less decrease in iron load from cardiac tissue. Pennell found that Deferiprone treated group exhibited significant improvement compared to Deferoxamine, with a reduced end-systolic volume and increased ejection fraction by cardiac MRI T2 images. [4,5]

Average monthly cost in Group A once/ month inj. for 16 patients was 4182; and per kg cost per patient per month was 53. Group B daily oral average monthly cost for 16 patients was 32280; per kg cost per patient per month was 478. Though not used in our trial, per kg cost for subcutaneous route at 20 mg/kg/day for 5/7days is 4920 plus pump cost 40000 (*table* 1, 2).

Side effects: one patient had developed chest tightness after 1 minutes of starting Deferoxamine infusion and patient was excluded from study, no side effects were observed in participants of both groups. In study by Cappellini Deferoxamine was administered to 277, Deferasirox to 276 over a period of two years; side effects were transient gastrointestinal events in 15.2% that included abdominal pain, nausea, vomiting, diarrhea, and constipation for a median of eight days or less; skin rash in 10.8%; deafness in eight patients on Deferasirox and seven on Deferoxamine and cataracts or lenticular opacities were reported in two patients on Deferasirox and five on Deferoxamine [5].

Results with intravenous Deferoxamine were better than tablet Deferasirox which is similar to study of Valymara et al (*table* 3). Effectiveness and safety of iron-chelation therapy with Deferoxamine or Deferiprone showed that Deferoxamine is stronger iron chelator in plasma [3].

Results were also similar to study by Cappellini on Iron chelation with Deferasirox in adult and pediatric patients with thalassemia major efficacy and safety during 5 years' follow-up. At the start of Deferasirox treatment, serum ferritin levels were generally lower in the crossover cohort in which patients had received 1 year of DFO treatment in the core study, compared with the Deferasirox cohort in which patients had started Deferasirox on entry to the study [6].

As per the search done in Google scholar for 7 pages in search engine; last study done for this topic was in 2011.

Conclusion:

We observed that Intravenous Deferoxamine is a better iron chelator with increased compliance even when used once a month as compared to the daily subcutaneous regimen; it not only decreases serum ferritin more rapidly than the Tablet Deferasirox but also more effectively . No adverse events were noted during our study.

***Limitation of Study*:**

Our study was done for six months and total of 32 patients were recruited. Baseline values of serum ferritin of both group had significant difference.

What is already known?

Reduction of Iron Overload in Thalassemia major: Regular Iron Chelators. In all studies done till now, Deferoxamine is either used alone or as combination therapy with Deferiprone. Tablet Deferasirox is administered every day and Intravenous Deferoxamine is administered subcutaneously 5/7 days a week by a pump.

Many patients had compliance issue due to daily regimen, cost, and multiple pricks 5/7 days a week along with pump cost.

What this Study Adds?

Efficacy: Intravenous Deferoxamine once a month is a better iron chelator than daily Tablet Deferasirox; it decreases serum ferritin more rapidly and more effectively.

Cost: Once a month Intravenous Deferoxamine is cheaper than the daily oral tablet Deferasirox or subcutaneous regimen with pump.

Acceptance and compliance to once a month intravenous route was high as no additional prick was necessary and patients got rid of daily tablet consumption.

Table 1 Change in Serum Ferritin Level

Ferritin level ng/ml					
	Inj Group A (n=16)		Tab Group B (n=16)		Inter Group p value
Time	Mean± SD	Intra Group p value	Mean ± SD	Intra Group p value	
Base	10850.12 ±3846.5		4879.18 ± 3086.9		<0.0001
2nd Month	10419.88 ±3585.1	0.74	4553.87 ±3081.3	0.76	<0.0001
4th Month	7774.5 ±2855.8	0.015	3816.93 ±2423.3	0.28	0.0002
6th Month	5508 ±1969.4	0.0001	3853.75 ±2095.6	0.28	0.02
Decrease in ferritin from base to 6 mo	5341.75 ± 3610.2	0.0001	1458.93 ± 1487.4	0.0014	

Table 2: Cost (in Rupees) Analysis

Group (n=16 each)	Average monthly cost per patient	Per kg cost per patient per month
A- once/ month inj.	246	8.2
B- daily oral	2760	90

*p=0.001

Subcutaneous route 5/7, per patient cost 1230 + pump cost 40000.

Table 3 Comparison with other studies

	Our study	Reference study
Route of Injectable	intravenous, once a month	subcutaneous; Olivier N. [2]
Frequency of dosage of injectable	Once every month 20-40 mg/kg over 7 hours ;one and half hour after blood transfusion	Dose used (Valymara), was 40-50 mg/kg/day once a day by subcutaneous route 8-12 hours injection 4-6 days/week [3]
Adverse events	1 patient developed chest tightness after 5 minutes of starting Deferoxamine infusion and was removed from study; no side effects were observed in other participants of both groups.	Many Adverse effects of gastrointestinal tract, skin, vision and hearing were observed; Cappellini M. [5]
Efficacy	Deferoxamine is more effective iron chelator as compared to oral Deferasirox	Iron chelation therapy with Deferoxamine or with Deferasirox was equally effective in decreasing iron burden; Walter PB [7]
Cost	Once monthly Deferoxamine is cheaper then daily Deferasirox.	Between Deferiprone and Deferoxamine, latter is cheaper; Walter PB [7]

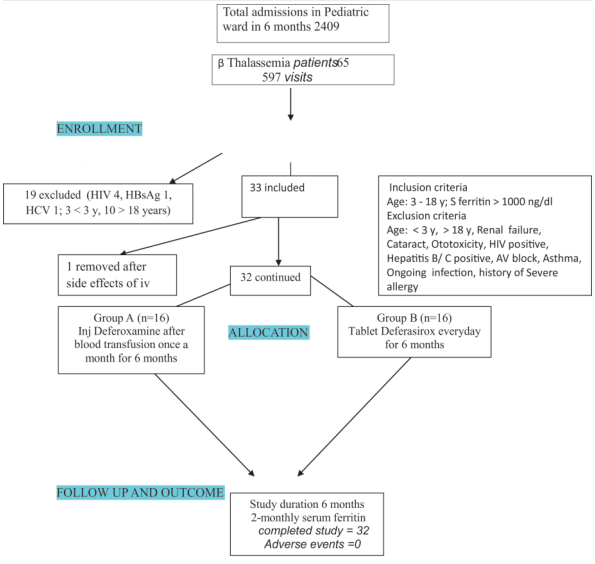
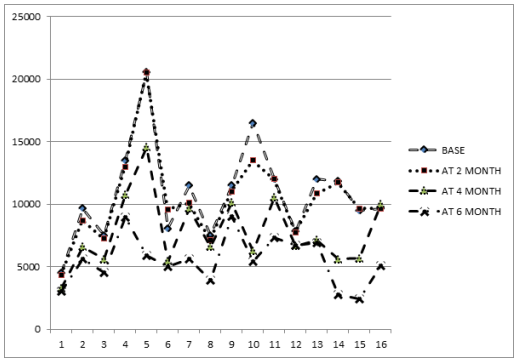
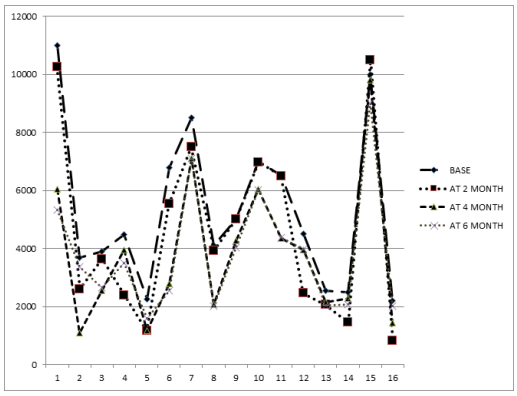


Fig 2: Change in Serum Ferritin, Group A (injection group)



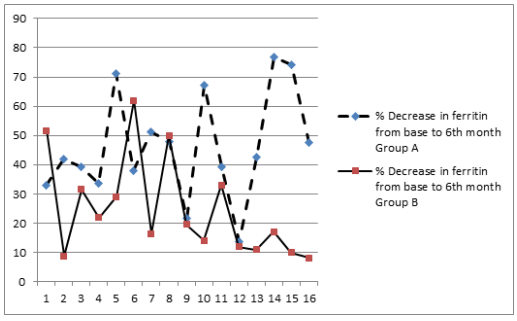
X = No. of patients; Y = serum ferritin in ng/ml

Figure 3: Change in serum ferritin level, Group B (oral group)



X = No. of patients; Y = serum ferritin in ng/ml

Figure 4: Decrease (%) in ferritin level from base to 6th month in both groups



X = No. patients; Y = % decrease in serum Ferritin; A = injection group; B = oral group

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