



Original Research Article

Study of serum ferritin level and effect of oral iron chelator in children with β -thalassemia majorUday N Vachhani¹, Chandrakant Kamariya^{2,*}¹Dept. of Biochemistry, GMERS Medical College, Himatnagar, Gujarat, India²Dept. of Biochemistry, PDU Medical College, Rajkot, Gujarat, India

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ABSTRACT

Objectives : To study the effect of oral iron chelator on serum ferritin level in patients with thalassemia major, we see the dose and frequency of oral iron chelator and its effect on serum ferritin and BT (Blood transfusion) iron overload.

Material and Methods: Patients with thalassemia with 5-18 year of age are taken in our study. Total numbers of patients taken are 50. 1st Group is with BT iron overload of 0.2-0.3mg/kg/day is given oral iron chelator in the dose 20mg/kg/day & serum ferritin should be <1500ng/ml. 2nd group is with BT iron overload of >0.3mg/kg/day is given oral iron chelator in the dose 30mg/kg/day & serum ferritin should be >1500ng/ml. Oral iron chelator is given according to serum ferritin level which is done at frequent intervals. Oral iron chelator is given as per serum ferritin level and maximum dose of oral iron chelator is 40 mg/kg/day. We study the dose of oral iron chelator, change in serum ferritin level and its effects on BT iron overload.

Results: Number of patients with BT iron overload in the range of 0.2-0.3 mg/kg is n=25(50%) in 1st Group. Number of patients with BT iron overload in the range of >0.3-0.4 mg/kg is n=15(30%) in 2nd Group. Number of patients with BT iron overload is more than 0.4 is n=10 (20%) in 3rd group. Calculated probability of average dose of oral iron chelator is <0.05 that means it is lower in 1st group than 2nd and 3rd group. There is significant decrease in serum ferritin level in 3 groups when we compare it with our beginning level (calculated probability <0.05). So, we can say that serum ferritin level is not depend on BT iron overload, but BT iron overload is depend on dose of oral iron chelator. Serum iron concentration is also lowered as there is increase in dose of oral iron chelator.

Conclusions: In our study we can say that oral iron chelator which can reduce serum ferritin level maximally was 30 mg/kg/day and showing very less side effects (BT iron overload taken for consideration was 0.3-0.4mg/kg/day). Oral iron chelator should be given less than 30mg/kg/day in patients having less BT frequency and less BT iron overload.

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1. Introduction

Oral iron chelator (Deferasirox) decreases deposited iron level in patients with beta thalassemia major, who are on frequent blood transfusion (BT). It is first started in USA (United States of America) for chelating agent in patients with iron overload.

Dose of oral iron chelator is one times a day in patient with overload of iron due to blood transfusion (BT iron overload). We monitor serum ferritin and dose of oral iron chelator is determined according to its level.^{1,2}

Liver iron concentration estimation is invasive and expensive procedure. Serum ferritin concentration estimation is non-invasive and low expensive procedure and can be used in place of liver iron concentration to assess BT iron overload. There is also correlation between liver iron concentration and ferritin level in various studies.³

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In thalassemia patients, oral iron chelator is given according to BT frequency. If patient is on <5 unit of BT/month, then we can give oral iron chelator in the dose of 20 mg/kg/day. If patients of thalassemia major are on more or less BT/month, then we can give higher or lesser dose of oral iron chelator (10 to 30 mg/kg/day). If BT iron overload is there, then dose adjustment should be done as per ferritin level.^{2,4–8}

If oral iron chelator is given in the range of 20–30 mg/kg/day, then we can get BT iron overload in the expected limit and prevent complications occurred due to deposited iron.^{4,5}

Relation between BT and iron overload can also present in various study carried out.^{4,9} Response to oral iron chelator is dependent on time at which treatment is initiated.

We have to give oral iron chelator as per TIF (Thalassemia International Federation) guidelines. Oral iron chelator is given in the dose of 20 mg/kg/day, if patient has BT iron overload in range of 0.3–0.5 mg/kg/day. If BT iron overload is less than this, then we can give dose less than 20mg/kg/day. If BT iron overload is more than this, then we can give dose up to or more than 30 mg/kg/day.² In our study, we measure serum ferritin level and changes in its level by oral iron chelator.

2. Materials and Methods

Our study is conducted in Civil Hospital in Saurashtra region. Number of thalassemic patients taken into study are 50. The age group we had selected is 5 to 18 years. Pre-consent has been taken from all the patients who are on the study. The most important investigation done in our study is measurement of serum ferritin. An inclusion criterion for study is: serum ferritin level = 1000 ng/dl. The following details are taken from thalassemic patients and recorded in the case report: (1) age (2) sex (3) weight (4) frequency and volume of BT (5) serum creatinine (6) AST (aspartate amino transferase) (7) ALT (alanine amino transferase) (8) serum ferritin (last three months mean). Exclusion criteria are (1) age <5 years (2) serum creatinine level >1.2 mg/dl (3) AST >40 IU/L (4) ALT > 40 IU. Oral iron chelator is given based on serum ferritin level. Oral iron chelator is given as a dose of 20 mg/kg/day if BT iron overload is 0.2–0.3 mg/dl and serum ferritin is <1500 ng/dl. Oral iron chelator is given in dose of 30mg/kg/day if BT iron overload is more than 0.3mg/kg/day and serum ferritin is >1500 ng/dl. Oral iron chelator is given as per serum ferritin level and maximum dose of oral iron chelator is 40 mg/kg/day. Investigations like serum ferritin, serum creatinine, AST and ALT are done at every 3 months. Oral iron chelator is withheld if patient reports shows (1) serum creatinine >1.2 mg/dl (2) AST>40 IU/L (3) ALT >40 IU/L.

2.1. Assessment and statistical methodology

BT iron overload is calculated by below given formula.^{2,9}

BT iron overload = no of BT in year X Volume of Red Blood cells in one BT X 60 X 1.08 / weight X 100

Unit for BT iron overload is in milligram. Packed cell volume in BT is 60% and iron in BT is 1.08/ml of Red blood cells.

In our study serum ferritin is also measures BT iron overload. Serum ferritin estimation done by ELISA (Enzyme-linked immunoassay) method on ELISA reader and washer.¹⁰ Serum ferritin estimation done at regular interval in all 3 groups to measure BT iron overload and dose of oral iron chelator can be changed as per the serum ferritin level.¹¹ Change in serum ferritin level and BT iron overload can be checked by Pearson's R (Pearson correlation coefficient) and calculated probability (p value).

3. Results

In our study, numbers of patients were 50. Sex ratio (male/female) is 38/12. Patient's weight was 15.35 kg (average). Patients age was 9 years (mean). Patients were diagnosed at an age of 12.80 (mean). Hemoglobin measured before starting BT was 6.4 gm % (mean). Patients were transfused in a year with red blood cells were 13.29 (number in average). BT in volume was 126 ml/kg/year. Number of patients with BT iron overload in the range of 0.2–0.3 mg/kg is n=25(50%) in 1st group. Number of patients with BT iron overload in the range of >0.3–0.4 mg/kg is n=15(30%) in 2nd group. Number of patients with BT iron overload is more than 0.4 is n=10 (20%) in 3rd group. Serum ferritin level before starting study was 1612 ng/dl (mean). Number of patients with serum ferritin level above 1500 ng/dl was n=44(88%). Number of patients with oral iron chelator given in the dose of 30 mg/kg/day were n=37(74%). Number of patients with oral iron chelator given in the dose of 20 mg/kg/day were n=13 (26%). Serum creatinine level before starting our study was 0.7 mg/dl. Serum AST level before starting our study was 52.01 IU/L. Serum ALT level before starting our study was 70 IU/L. (Table 1).

Calculated probability is < 0.05 (p value) in 1st group patients than 2nd group and 3rd group patients, if we compare beginning dose of oral iron chelator. As study progress, there is increment in oral iron chelator dose in all 3 groups when we compare it with our beginning dose (calculated probability <0.05). Calculated probability of average dose of oral iron chelator is <0.05 that means it is lower in 1st group than 2nd group and 3rd group (Table 2).

Calculated probability is <0.05 in 1st group patients when we compare it with 2nd group and 3rd group patients based on serum ferritin level and it is higher in 2nd group and 3rd group. As study progress, there is significant decrease in serum ferritin level in all 3 groups when we compare it with our beginning level (calculated probability <0.05).

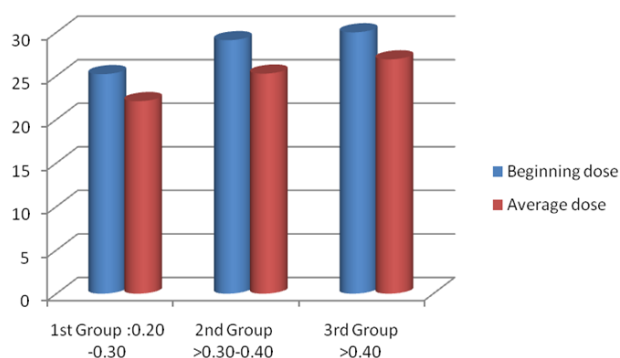
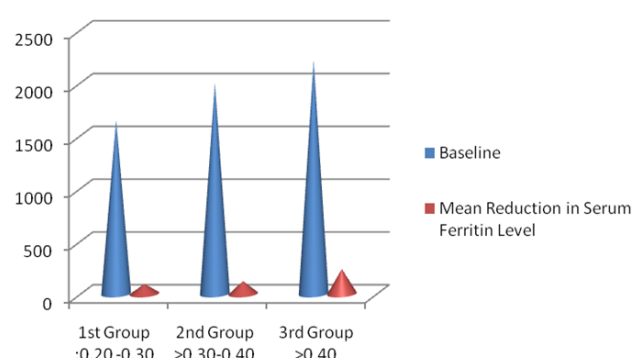
Table 1: Baseline parameters. (n=50)

Age group (mean)	9±3.39
Sex Ratio (male/female)	38/12
Patient's weight (average)	15.35±6.2
Hemoglobin measured before starting BT	6.4±0.3
Thalassemia diagnosis age (Mean)	12.8±3.31
BT in a year (Number in average)	13.29±3.42
BT in volume in ml/kg/year	126
BT iron overload in mg/kg/day	0.33
BT iron over loading in mg/kg/day	
1 st Group: 0.2-0.3	n=25 (50%)
2 nd Group: >0.3-0.4	n=15(30%)
3 rd Group: >0.4	n=10 (20%)
Serum ferritin in ng/ml(mean baseline)	1612±309.12
=>1000-1500	n=6(12%)
>1500-2500	n=40 (80%)
>2500	n=4 (8%)
Oral Iron chelator in mg/kg/day (beginning dose)	
20	n=13 (26%)
30	n=37 (74%)
serum creatinine (mean beginning)	0.7mg/dl
ALT & AST (mean beginning)	52.01,70IU/L

Table 2: Mean prescribed dose of deferasirox in children with β - thalassemia major (n=50).

BT iron overload (ml/kg/day)	Number of patients	Follow up Beginning dose	Average dose
1 st Group :0.20 -0.30	25	25.2±5.1	22.1±2.10
2 nd Group >0.30-0.40	15	29.1±4.01*	25.26±3.18*
3 rd Group >0.40	10	30.00±0*	26.9±2.1*

*Value significant as compared to 1st Group (p<0.05).

**Fig. 1:** Mean prescribed dose of deferasirox in beta thalassemia patients.**Fig. 2:** Mean serum ferritin in children with beta thalassemia on oral iron chelator

The percentage decrease in serum ferritin level was 16%, 6.8% and 16.5 in all 3 groups (Table 3).

Perasons R was 0.53 and calculated probability was 0.0006 in patients when BT frequency increase and oral iron chelator demand increases. These relations are linear. Perasons R was 0.0022 and calculated probability was 0.85 in patients when BT frequency increase and serum ferritin

level doesn't fall according to increase demand of BT. These relations are not linear. So, we can say that serum ferritin level is not depend on BT iron overload, but BT iron overload is depend on dose of oral iron chelator. Serum iron concentration is also lowered as there is increase in dose of oral iron chelator.¹²

Table 3: Mean serum ferritin in children with B-thalassemia major following treatment with oral iron chelator (n=50). Mean serum ferritin(ng/ml)

BT iron overload (ml/kg/day)	Number of patients	Follow up	
		Baseline	Mean Reduction in Serum Ferritin Level
1 st Group :0.20 -0.30	25	48± 312.08	94.8± 190.12
2 nd Group >0.30-0.40	15	98.28± 612.22*	121.26± 202.10
3 rd Group >0.40	10	212.16± 302.25 *	236.14± 111.16

*Value significant as compared to 1st Group (p<0.05)

In our study, we can say that there is not a linear relationship between BT iron overload and reduction in serum ferritin level. Oral iron chelator has very good effects on BT iron overload and number of patients having adverse drug reaction is negligible.¹³ Percentage of patients in which main complaint was abdominal pain was only 4%. Percentages of patients stick to therapy are 95%.

4. Discussion

Our study correlates with study done by Sankar et al showing male patients more than female patients.¹⁴ Demographic profile like age correlates well with study done by Indian studies showing 13 years as mean age.¹⁴ Study done by Desai et al showing BT frequency of 180 ml/kg/year which is higher than our study.⁷ BT frequency determines iron deposition in body and it is well correlates with it.² In our study BT frequency was only 126 ml in year, so iron deposition remains less than 0.4 mg/kg/day. Serum ferritin Concentration is a sensitive measure of body iron store. Study done by Rohner et al showing manual and automated ELISA method comparison for serum ferritin estimation elaborates importance of estimation of serum ferritin.^{10,11} Shah et al showing serum ferritin level (mean) is well correlates with study done by us and it is more than 1500 ng/ml.^{15,16} Study done by Erika et al showing beginning dose of oral iron chelator well correlates with study done by us and it is more as BT iron overload increases. Oral iron chelator in the dose of 30 mg/kg/day is sufficient in patients to achieve maximum effects and minimize iron deposition and its post deposit effects.^{4,16} Study done by El-Beshlawy et al showing mean reduction in serum ferritin level after giving dose of oral iron chelator (20-30 mg/kg/day) was 198 ng/ml and it is correlates well with our study showing reduction in serum ferritin level (236 ng/ml) when oral iron chelator given for one year (26 mg/kg/day).⁸ Patients on 2nd and 3rd group with oral iron chelator showing very good reduction in serum ferritin level compared to 1st group in our study and also study done by Emanuele et al. Dose of oral iron chelator for maximum reduction in serum ferritin level was 20-30mg/kg/day, which is well tolerated and with less chances of adverse drug reaction and maximum effects.^{13,17} BT iron overload and serum ferritin level doesn't showing linear relationship in

our study, it is due to only serum ferritin level taken as consideration for measuring BT iron overload and no other parameter taken for consideration.⁷ Study done by Dhamija et al showing effect of oral iron chelator and chances of adverse drug reaction well correlates with our study and percentage of patients remain stick to therapy was 96%.^{13,18}

5. Conclusion

In our study we can say that oral iron chelator which can reduce serum ferritin level maximally was 30 mg/kg/day and showing very less side effects (BT iron overload taken for consideration was 0.3-0.4mg/kg/day). Oral iron chelator should be given less than 30mg/kg/day in patients having less BT frequency and less BT iron overload. A linear correlation between oral iron chelator and BT iron overload and non-linear correlation between BT iron overload and serum ferritin level means we have to monitor serum ferritin and dose of oral iron chelator is decided according to its level.

5.1. Authors Contribution

Conception or design of the work: Dr. Uday
Data collection: Dr. Chandrakant
Data analysis and interpretation: Dr. Uday, Dr. Chandrakant
Drafting the article: Dr. Uday
Critical revision of the article: Dr. Uday, Dr. Chandrakant
Final approval of the version to be published: Dr. Uday, Dr. Chandrakant

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6. Source of funding

None

7. Conflict of interest

None.

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