Barriers to Adherence to Iron Chelation Therapy in Thalassemia Patients

Abstract
Background: Thalassemias are the most common inheritable blood disorders requiring regular blood transfusions and iron chelating therapy. Non-adherence to iron chelation therapy increases complications and is a problem in treating thalassemia. To assess the reasons of non-adherence to iron chelating drug in treating thalassemia.

Materials and methods: This descriptive cross-sectional study was carried out in the thalassemia ward of Chattogram Maa Shishu-O-General Hospital, Chattogram from July, 2013 to June, 2014. 70 thalassemia patients aged 2-18 years previously treated with iron chelating drugs were included. Parents were interviewed according to a formulated questionnaire based on discontinuation of iron chelating drugs and its reasons. Data were analyzed by both manually and by SPSS-18.

Results: About 48.6% patients needed blood transfusion >10 units/year and 62.9% patients were prescribed with iron chelating drugs. Near about half patients (47.7%) did not continued iron chelating therapy till full prescribed period. Deferiprone (31.8%) and combination of deferiprone & desferrioxamine (31.8%) was the most commonly prescribed drug. Deferiprone is the drug to which most of the patients (70%) were adherent and a good number of patients (65%) discontinued desferrioxamine. Financial problem (100%) was the only reason for discontinuation of oral chelator. In case of parenteral chelator, besides financial problem (38.5%), time consuming natures (38.5%), need of hospital admission (23%) are the other causes for non-adherence to iron chelation therapy.

Conclusion: Financial problem is the main cause of non-adherence to iron chelation therapy. Iron chelating drugs should be available at low cost.

Key words: Iron chelating drugs; Non-adherence; Thalassemia.

INTRODUCTION
Thalassaemias are a heterogeneous group of genetic disorders of human haemoglobin synthesis, characterized by imbalanced globin chain production which leads to ineffective erythropoiesis and anaemia1. There are an estimated 270 million individuals worldwide who are carriers of globin gene mutations2. A conservative WHO report estimates that 3% of total population is carrier of β-thalassemia and 4% are carriers of Hb E in Bangladesh and more than two thousand thalassemic children are born every year3,4.

The clinical picture of thalassemia major is characterized by growth retardation, pallor, jaundice, hepato-splenomegaly, skeletal changes that needs regular blood transfusion at 3-4 week interval to maintain Hb level of at least 9-10mg/dl to improve growth and development, to reduce bone deformities and also to prevent hepato-splenomegaly due to extramedullary hematopoiesis5-9. Iron chelating drugs
are needed as regular blood transfusion results in iron overload and related complication such as dilated cardiomyopathy, liver cirrhosis, endocrine problem and others. Individuals who have not been regularly transfused usually die before 2nd–3rd decade. Survival of individuals who have been regularly transfused and treated with appropriate chelation extends beyond the age of 40 years. In a study of an Italian cohort reported that with optimal iron chelation therapy, 68% thalassemia patients lived to the age of 35 years. In our country iron chelators in current clinical use are subcutaneous or intravenous desferrioxamine, oral deferiprone and oral deferasirox. Desferrioxamine is most commonly administered as a subcutaneous infusion over 8–10 hours, 3–6 nights weekly. But compliance with iron chelating therapy is a major issue. Compliance with iron chelating therapy mainly influences frequency and severity of the iron-overload related complication. In a substantial proportion of patients in routine clinical practice, adequate control of tissue iron levels is not achieved due to non-compliance and poor adherence to iron chelating therapy. Adherence is poor in majority of the patients for various reason including higher costs, discomfort, time consuming nature, unavailability, forgetfulness. The adherence to treatment, the ease and satisfaction from their therapy differs according to type, route of administration of iron chelating drugs. In a study in Australia the duration and discomfort of the infusion was the main issue for non-adherence to iron chelating therapy and higher adherence rates were identified for oral deferiprone, especially in patients with poor desferrioxamine adherence, suggesting that the mode of administration plays a major role. In some countries, difficulty of access to iron chelating medications is a significant reason for non-compliance. Wider availability of oral medications is likely to improve adherence and subsequent health outcomes. It is very common in some developing countries that patients are undertreated or irregularly transfused and poorly adherent to iron chelator due to lack of resources. The barriers to adherence to iron chelation therapy in thalassemia patients have not been well studied in our country. We have conducted this study to address these barriers so that measures can be taken to overcome the barriers.

To assess the reasons of non-adherence to iron chelating drugs in treating thalassemia

**MATERIALS AND METHODS**

It was a descriptive cross-sectional study conducted at Chattogram Maa Shishu-O-General Hospital, Chattogram from July, 2013 to June, 2014. 70 thalassaemia patients aged 2-18 years previously treated with iron chelating drugs attending Thalassaemia Care Centre of Paediatric ward of Chattogram Maa Shishu-O-General Hospital, Chattogram with history of intake of iron chelation therapy were included. All newly diagnosed cases were excluded. After approval from the Ethical Review Committee of Chattogram Maa Shishu-O-General Hospital, Chattogram, informed written consent was obtained from any of parents or a family member of each patient. Detailed study related information was read out and explained in the local language from a printed hand out. Parents were interviewed according to a formulated questionnaire asking the type of iron chelating drugs prescribed and reasons for discontinuation. Data were checked and analyzed manually with the help of calculator and software SPSS 18.0 according to the objective of the study. All aspects of confidentiality of participant were maintained and anyone was allowed to discontinue if he or she wanted.

**RESULTS**

Regarding treatment history, 25.7% needed blood transfusion less than 5 units/year, another 25.7% needed 5–10 units/year and nearly half patients (48.6%) needed more than 10 units/year. About 62.9% patients were prescribed with iron chelation therapy. Of them, 31.8% patients were prescribed with DFN only, another 31.8% were prescribed with DFO & DFN co-prescription, 4.5% with alternate DFN & DFX, 18.3% patients were prescribed with DFX only and 13.6% with DFO & DFX co-prescription. So most commonly prescribed iron chelation therapy was DFN single drug and DFO & DFN co-prescription. Splenectomy was done previously only in 5.7% patients but no one was able to afford bone marrow transplantation (Table I).

**Table I : Patient’s treatment profile (n = 70)**

| Treatment Profile                  | Frequency | Percentage (%) |
|-----------------------------------|-----------|----------------|
| Need blood transfusion            |           |                |
| < 5 times/year                    | 18        | 25.7           |
| 5 – 10 times/year                 | 18        | 25.7           |
| > 10 times/year                   | 34        | 48.6           |
| Iron Chelating Agent (ICT)        |           |                |
| Yes                               | 44        | 62.9           |
| No                                | 26        | 37.1           |
| Iron chelating agent prescribed (n = 44) |          |                |
| DFN only                          | 14        | 31.8           |
| DFO + DFN co-prescription         | 14        | 31.8           |
| DFN & DFX alternately             | 2         | 4.5            |
| DFX only                          | 8         | 18.3           |
| DFO + DFX co-prescription         | 6         | 13.6           |
| Splenectomy done                  |           |                |
| Yes                               | 4         | 5.7            |
| No                                | 66        | 94.3           |
| Can afford bone marrow transplantation |    |                |
| Yes                               | 0         | 0.0            |
| No                                | 70        | 100.0          |

* ICT = Iron Chelating Therapy
Out of 44 patients prescribed with different type ICT and combination, only 52.3% continued it for full prescribed period (Table II). Highest adherence was found to DFN (70%) and lowest adherence was found to DFO (35%) (Table II). The only cause of non-adherence to DFN and DFX was financial problem. The common causes of discontinuation of DFO were time consuming nature of parenteral infusion, financial problem and need of hospital admission for infusion (Table III).

**Table II :** Treatment profile and adherence of iron chelating therapy (ICT)

| Iron Chelating Therapy (ICT) | Frequency | Percentage (%) |
|-----------------------------|-----------|----------------|
| Adherence to ICT (n = 44)    |           |                |
| Full adherence               | 23        | 52.3           |
| Non-adherence                | 21        | 47.7           |
| Adherence of patients prescribed with DFN (n=14) | | |
| Continued                    | 10        | 71.4           |
| Discontinued                 | 4         | 28.6           |
| Adherence of patients prescribed with DFO+DFN co-prescription (n = 14) | | |
| Both continued               | 5         | 35.7           |
| DFN continued, DFO discontinued | 4     | 28.6           |
| DFO continued, DFN discontinued | 0        | 0.0            |
| Both discontinued            | 5         | 35.7           |
| Adherence of patients prescribed with DFN & DFX alternately (n = 2) | | |
| Both continued               | 2         | 100.0          |
| DFN continued, DFX discontinued | 0     | 0.0            |
| DFX continued, DFN discontinued | 0        | 0.0            |
| Both discontinued            | 0         | 0.0            |
| Adherence of patients prescribed with DFX (n = 8) | | |
| Continued                    | 4         | 50.0           |
| Discontinued                 | 4         | 50.0           |
| Adherence of patients prescribed with DFO+DFX co-prescription (n = 6) | | |
| Both continued               | 2         | 33.3           |
| DFX continued, DFO discontinued | 1     | 16.7           |
| DFO continued, DFX discontinued | 0        | 0.0            |
| Both discontinued            | 3         | 50.0           |
| Overall DFN adherence (n = 30) | | |
| Continued                    | 21        | 70.0           |
| Discontinued                 | 9         | 30.0           |
| Overall DFX adherence (n = 16) | | |
| Continued                    | 9         | 56.2           |
| Discontinued                 | 7         | 43.8           |
| Overall DFO adherence (n = 20) | | |
| Continued                    | 7         | 35.0           |
| Discontinued                 | 13        | 65.0           |

DFN = Deferiprone, DFX = Deferasirox, DFO = Desferrioxamine.

**Table III :** Causes of non-adherence of iron chelating agents

| Cause of Non-adherence | Frequency | Percentage (%) |
|------------------------|-----------|----------------|
| Non-adherence to DFO (n = 13) | | |
| Time consuming         | 5         | 38.5           |
| Financial problem      | 5         | 38.5           |
| Need admission         | 3         | 23.0           |
| Not available          | 0         | 0.0            |
| Forgetfulness          | 0         | 0.0            |
| Non-adherence to DFN (n = 9) | | |
| Financial problem      | 9         | 100.0          |
| Not available          | 0         | 0.0            |
| Forgetfulness          | 0         | 0.0            |
| Non-adherence to DFX (n = 7) | | |
| Financial problem      | 7         | 100.0          |
| Not available          | 0         | 0.0            |
| Forgetfulness          | 0         | 0.0            |

DFN = Deferiprone, DFX = Deferasirox, DFO = Desferrioxamine.

**DISCUSSION**

In our study, 25.7% patients need blood transfusion <5 unit per year, another 25.7% need 5-10 unit year, 48.6% patients need up to >10 unit per year. Similarly, 23.7% received up to 5 unit/year, 29.66% up to 6-10 unit/year, 30.4% received 11-15 unit blood transfusion per year in a study of Mallik S et al22. We had only 5.7% splenectomized patient that is similar to that study22. None was able to afford bone marrow transplantation but in Pakistan near about 5% family were ready for bone marrow transplantation of their child23. Monotherapy DFN (31.8%) and combination of DFO & DFN (31.8%) were the highly prescribed drugs in our study. A worldwide survey reported that mono therapy with desferrioxamine (DFO) was the most widely used drug in the world and deferiprone (DFP) monotherapy and DFO & DFP combination were more common in Europe and the Middle-East/Africa than in the Asia-Pacific region24. In our study, 52.3% of our patients prescribed with ICT continued it for full prescribed period and highest adherence was found to DFN (70%) and lowest to DFO (35%). Lowest adherence to DFO also reported by Arif F et al and highest adherence to DFN by Kidson GL et al25,19. Compliance were unsatisfactory also in Srilanka26. Adherence rate was more better in North America where average adherence were 92.2% for DFO and 95.5% to oral chelator (95.5%=DFX, 94.5% DFN) and 76.1 % of DFX and 87.8% of DFN showed at least 90% adherence respectively but in Australia majority showed <50% adherence and a few >90% adherence27,19. Higher adherence rate to DFN in our study may be due to low cost of DFN. Similar to the reports of Olivieri NF et al, we found rate of non-adherence to ICT was highest for DFO (65%) followed by DFX (43.8%), DFN (30%)28. Major cause of non-adherence to...
DFO was time consuming procedure (38.5%) and financial problem (38.5%) followed by cumbersome process that need hospital admission (23%) suggesting along with financial problem mode of administration and need of hospital admission play a great role for adherence to DFO. Besides, financial problem was the only reason for discontinuation of DFN and DFX. In Australia financial problem was not an issue for non-adherence, too busyness of parents and discomfort of pump infusion reported as most common reason of DFO non-compliance. An international survey reported that access to the drug was the most common cause of non-adherence in India (51%), Iran (25%) and other countries (<17%). In some countries, false beliefs or feelings about the medication and drug related side effects is a common factor for non-compliance. In our study it is not a factor as we have a Thalassemia Care Center in our hospital for special care of thalassemia patients for which reason most of drugs needed to treat thalassemia patient are available at our hospital pharmacy. So oral ICT should be available free of cost at government setting as well as at NGO level.

LIMITATIONS

- This was a cross-sectional study where only 70 patients were included.
- Limited period of study for one year only.
- Data were collected only from one hospital.

CONCLUSION

Non-adherence to iron chelating drugs is quite common problem in our country. Cost of iron chelating drugs is the main reason for non-adherence followed by time consuming nature, need of hospital admission. Patient’s concern for choosing drugs should be considered for better adherence especially in patients with poor socio-economic condition. As thalassemia is great health and economic burden to a family as well as to the society, health policy makers should take necessary step to make iron chelating drugs available at free of cost for improving the lives of patients.

DISCLOSURE

All the authors declared no competing interest.
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