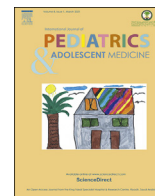


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Original article

Prescribing patterns and drug-related problems (DRPs) in transfusion-dependent paediatric thalassemia patients: A prospective interventional study from a tertiary care hospital in India

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ABSTRACT

Background: Each year nearly 10,000 children with thalassaemia major are born in India, but among them, very few are optimally managed mainly in urban regions even though the Government of India has incorporated their care and treatment in the 12th Five-Year Plan. Data on prescribing patterns and drug-related problems (DRPs) in paediatric thalassaemia patients in India are limited.

Methods: In this prospective interventional study, the medications prescribed were recorded after reviewing the treatment charts, thalassaemia register, thalassaemia card, nurses' notes, as well as discharge summaries. When DRPs and/or medication errors were identified, the same was discussed with the concerned health care professionals and suitable suggestions were made at the earliest.

Results: Out of the enrolled 54 patients, only 94% (n = 51) of the patients received iron chelation therapy with deferasirox and/or deferiprone, Folic acid tablet was prescribed for 100% of the patients (n = 54). Five percent of patients (n = 3) had undergone splenectomy and was prescribed with amoxicillin prophylactically. There were a total of 16 DRPs and 15 medication errors were identified and suitable measurements were taken to solve these problems.

Conclusions: The prescribing patterns, DRPs and medication errors in transfusion-dependent paediatric thalassaemia patients were discussed in this study. Our study was effective in identifying and solving the DRPs and medication problems that occurred in thalassaemia patients.

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1. Introduction

The thalassaemias are a group of hereditary blood disorders that result in the defective synthesis of one or more of the haemoglobin chains. Alpha and beta thalassaemias are characterised by the decreased or absent synthesis of alpha and beta globin chains. Imbalances of globin chains cause haemolysis and impair erythropoiesis [1,2]. Thalassaemia disorder was classified previously as major, intermediate, or minor genotypes but recently the thalassaemia disorder was classified based on the transfusion requirement of patients as transfusion-dependent thalassaemia (TDT) and non-transfusion-dependent thalassaemia [3]. Transfusion-induced

iron overload happens in thalassaemia patients as the human body has no physiological mechanism to remove excess iron from multiple transfusions. So the TDT patients need management with iron-chelating agents as it forms complexes with iron [4–6]. The iron chelators such as deferoxamine, deferiprone and deferasirox have been licensed for clinical use as monotherapies. Combination therapies may theoretically improve chelation efficiency by increasing the rate of access to intracellular iron pools or to plasma non-transferrin bound iron [1,7].

In our hospital, the standard practice is to initiate iron chelation therapy in thalassaemia patients, if the transfusion is more than or equal to 100 ml/kg of packed red blood cells and the serum ferritin levels are consistently greater than 1000 mcg/L. The initial dose of deferasirox is 20 mg/kg, once in a day and the dose is then modified at 3–6 month intervals depending on the serum ferritin levels; the dose is modified by 5 or 10 mg/kg/day; and titration of the dose during modification is based on the individual response and

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treatment goals. In patients not adequately controlled with 30 mg/kg/day, doses up to 40 mg/kg/day may be recommended if serum ferritin is consistently more than 2,500 mcg/L and not reducing over time. According to the World Health Organisation (WHO) guidelines, the maximum dose of deferasirox recommended for the treatment of thalassaemia is 40 mg/kg/day. Deferasirox is recommended for the management of thalassaemia patients who are older than 2 years of age [8,9]. In our hospital, the thalassaemia patients are on dispersible deferasirox tablet, so it is administered as a suspension in water or apple juice on an empty stomach [8,10]. Additionally, deferiprone was also added in those TDT patients who showed an inadequate response to deferasirox therapy and its initial dose is 25 mg/kg 3 times/day (75 mg/kg/day). Deferiprone dose was individualised based on the response of the patient and therapeutic goal. The maximum dose of deferiprone recommended is 33 mg/kg 3 times/day (99 mg/kg/day) [8]. Although treatment with deferoxamine is effective, its infusions are time-consuming, expensive and painful in children. Deferoxamine has a negative impact on the patient's quality of life [11]. Therefore, the treatment with deferoxamine is not practised in our institution. Folic acid is administered daily (2.5 mg–5 mg, PO) in thalassaemia patients as its deficiency has been reported due to increased erythropoiesis in them [1]. Amoxicillin was administered prophylactically (250 mg, PO, once daily) to the thalassaemia patients who have undergone splenectomy [12].

Thalassaemia clinic is not a widely practised clinical speciality in India; few hospitals in India have thalassaemia clinics. This study aimed to assess the prescribing patterns and to determine the DRPs in the transfusion-dependent paediatric thalassaemia patients from a tertiary care hospital in India.

2. Methods

2.1. Study design and setting

This study followed a prospective interventional design including prescribing patterns and DRPs among transfusion-dependent paediatric thalassaemia patients; it was conducted in the Haematology and Thalassaemia Clinic of the paediatric department (120 beds) of a multi-speciality teaching hospital in India from November 1st 2018 to January 31st 2019. The Haematology and Thalassaemia Clinic will function every day and 54 transfusion-dependent paediatric thalassaemia patients were on treatment under this clinic. The study protocol was approved by the institutional ethics committee of JSS Medical College, Mysore.

2.2. Study procedure

TDT patients admitted to the paediatric ward for their regular blood transfusions during the study period were identified daily by the researchers using the wards' census registers. After information about this study was given, written informed consent was obtained from the participants and from their parents. The admission notes, outpatient records, discharge summaries from previous hospitalisations, demographics, and medical histories were reviewed on the day of patient inclusion. The thalassaemia patients and their caregivers were interviewed for the clarification of medical history information. Medications prescribed were recorded after reviewing the treatment charts, thalassaemia register, thalassaemia card (each patient is provided with a separate card, which contains data about the patient's medications, serum ferritin, haemoglobin, and packed cell volume), nurses' notes, as well as discharge summaries into the data collection form designed for the study. Data collected were keyed into a specially designed Microsoft Access Database (Microsoft Corporation, Redmond, Washington).

When DRPs and/or medication errors were identified by the researchers, the same was discussed with the clinical pharmacist, postgraduate students, resident doctors, and the unit chief of the paediatric department. The suitable suggestions were made regarding the identified DRPs and/or medication errors at the earliest possible time and were documented in the data collection form. To check the quality of the documentation and also to minimise transcription errors, clinical pharmacists and paediatricians reviewed the data collection forms for ensuring the consistency of information transferred from patients' medical records. DRPs identified were categorised based on categories described by Hepler and Strand as follows: untreated indication, improper drug selection, sub-therapeutic dose, overdose, adverse drug reactions (ADRs), drug interactions, failure to receive drugs and drug use without indication [13]. Medication errors identified were categorised according to the National Coordinating Council for Medical Error Reporting and Prevention (NCC MERP) Index and classified according to where they occur in the medication use cycle [14,15].

3. Results

Over the 3-month study period, 54 patients (63% male, 37% female) were enrolled (Table 1). Among the enrolled patients, 2% (n = 1) was diagnosed as transfusion-dependent alpha thalassaemia and 98% (n = 53) of the patients were diagnosed as transfusion-dependent beta thalassaemia.

3.1. Prescribed medications

Out of the 54 enrolled patients, 94% (n = 51) received iron chelation therapy with deferasirox and/or deferiprone and 6% (n = 3) of the patients did not receive iron chelation therapy. Mono chelation therapy with deferasirox was prescribed for 83% of the patients (n = 45). The combination of iron chelation therapy (deferasirox + deferiprone) was prescribed for 11% (n = 6) of the patients. Folic acid tablet was prescribed for 100% of the patients (n = 54). Five percent of patients (n = 3) had undergone splenectomy and were prescribed with amoxicillin prophylactically.

3.2. Prescribed dose of medications

The prescribed dose of deferasirox for mono chelation therapy ranges from 20 mg/kg to 40 mg/kg. In combination chelation therapy with deferasirox and deferiprone, the deferasirox dose ranges from 25 to 30 mg/kg/day (once daily or twice daily) and the deferiprone dose of 25 mg/kg/dose is administered 3 times a day. The dose of folic acid ranges from 2.5 to 5 mg per day and the dose of amoxicillin is 250 mg per day.

3.3. Drug-related problems and medication errors

There were a total of 16 DRPs and 15 medication errors identified after reviewing the treatment chart and interviewing the 54 recruited patients and/or caregivers over a period of 3 months. From the 16 DRPs, 3 were categorised under "sub-therapeutic

Table 1
Demographics of the study patients.

Age (years)	Number of patients	Gender		Total percentage (%)
		Male	Female	
2–5	11	6	5	20
5–10	25	15	10	46
11–18	18	13	5	34

dose”, 5 were under “ADRs” and 8 were under “failure to receive drugs” (Table 2). Out of the 15 medication errors, all medication errors were under category D and classified under administration errors: 8 medication errors were under the inappropriate technique of administration and 7 medication errors were under the inappropriate time of administration (Table 3).

3.4. Assessment, classification, preventability and severity of ADRs

The causality of ADRs was assessed by using ADR causality assessment scales, such as Naranjo and WHO Uppsala Monitoring Centre (UMC) [16,17]. Preventability of ADRs was assessed by using Modified Schumock and Thornton criteria [18]. The severity of ADRs was assessed by using Modified Hartwig and Siegel scale [19]. The ADRs were classified by using Rawlins and Thompson classification (Table 4) [20].

4. Discussion

This study provides further information on prescribing patterns, DRPs and medication errors in transfusion-dependent paediatric thalassaemia patients. Iron-chelating agents were not prescribed for 6% ($n = 3$) of the enrolled patients, because there was no evidence of chronic iron overload in these patients (Generally, iron chelation therapy should only be initiated with the evidence of chronic iron overload that is transfusion of more than or equal to 100 ml/kg of packed RBCs and serum ferritin levels consistently greater than 1000 mcg/L) [8,9]. Mono chelation therapy with deferasirox was prescribed for 83% ($n = 45$) of the patients to reduce their serum ferritin levels. The combination chelation therapy with deferasirox and deferiprone was prescribed for 11% ($n = 6$) of the patients as their serum ferritin levels were not controlled with the deferasirox mono chelation therapy despite receiving the maximum daily dose of deferasirox (40 mg/kg/day). The mono and combination iron-chelating agents prescribed to the

transfusion-dependent paediatric thalassaemia patients in our hospital is in accordance with the guidelines [8,9]. All the patients received tablet folic acid at a dose of 2.5–5 mg per day as a result of increased erythropoiesis [1]. Out of the 54 patients, 3 patients had undergone splenectomy and were administered with tablet amoxicillin prophylactically (250 mg per day) [12].

Among the 16 DRPs identified, the highest number of DRPs falls under “failure to receive drug”, followed by “ADRs” and “sub-therapeutic dose”. The reasons for failure to administer the drug (Deferasirox) were as follows: First, because of the unpleasant taste of the suspension made by dissolving the deferasirox tablet in water. Second, because of the unawareness of the parents and children regarding the importance of iron chelation therapy and complications of iron overload. The adverse reaction arthralgia due to deferasirox was reduced after changing once daily deferasirox dosing to twice-daily deferasirox dosing with the same total dose, as this dosing is effective in iron chelation and improved tolerability in the patient due to various pharmacokinetic advantages of the twice-daily dosing of deferasirox [21]. The adverse reactions nausea and vomiting were resolved after dissolving deferasirox tablet in orange juice or apple juice instead of dissolving in water for its administration to mask the unpleasant taste of the suspension. There were no actions taken for the other ADRs that occurred, considering the non-severe nature of the ADRs and also that the adverse reactions resolved by themselves [19]. The medication errors occurred due to an inappropriate method and the time of administration of deferasirox, as the patients and caregivers were unaware of it. All medication errors were under category D because the error occurred had reached the patient and needed monitoring to justify that it resulted in no harm to the patient and/or required intervention to preclude harm [14,15].

The limitation of this study included a small sample size of 54 patients. This was the first study of its kind and we could not compare it with other literature.

Table 2
DRPs Identified, Category, Action taken against the DRPs and Outcomes.

Sl. no.	DRPs identified	Category	Action taken against the DRPs	Outcome
1	The patient ferritin levels were consistently above 2500 mcg/L and received deferasirox 25 mg/kg/day.	Sub-therapeutic dose	The dose of deferasirox was increased by 10 mg/kg/day.	On follow up after 3 months, the serum ferritin level was reduced to 1940 mcg/L.
2	In another patient, the serum ferritin levels (1800 mcg/L, 2200 mcg/L) were not controlled after receiving deferasirox 20 mg/kg/day.	Sub-therapeutic dose	The dose of deferasirox was increased by 5 mg/kg/day.	On follow up after 3 months, the serum ferritin level was reduced to 1600 mcg/L.
3	The patient ferritin levels were consistently above 2500 mcg/L and received deferasirox 30 mg/kg/day.	Sub-therapeutic dose	The dose of deferasirox was increased by 10 mg/kg/day.	On follow up after 3 months, the serum ferritin level was reduced to 2000 mcg/L.
4	The patient complained of dizziness after taking deferasirox tablet but resolved after 5–10 min.	ADR	No action taken, considering the non-severe nature of ADR and the ADR resolved by itself.	On follow up after 3 weeks, the frequency of dizziness occurrence reduced and after 6 weeks, the patient had no complaints of dizziness.
5	The patient complained of dizziness after taking deferasirox tablet, but resolved after 10 min.	ADR	No action taken, considering the non-severe nature of ADR and the ADR resolved by itself.	On follow up after 1 month, the patient had no complaints of dizziness.
6	The patient complained of nausea after taking deferasirox tablet because of its unpleasant taste.	ADR	Advised to dissolve the deferasirox tablet in orange juice or apple juice, instead of dissolving in water for its administration.	On follow up after 2 weeks, the patient had no complaints of nausea.
7	The patient complained of vomiting after taking deferasirox tablet because of its unpleasant taste.	ADR	Advised to dissolve the deferasirox tablet in orange juice or apple juice instead of dissolving in water for its administration.	On follow up after 2 weeks, the patient had no complaints of vomiting.
8	A patient complained of arthralgia for 1 month and his pain score was 5 at that time according to a 1–10 pain scale.	ADR	Advised to change the once-daily dosing of deferasirox to twice daily dosing with the same total daily dose.	On follow up after 3 months, his pain was reduced with a pain score of two according to a 1–10 pain scale.
9	Eight patients did not take the prescribed medications (Deferasirox).	Failure to receive drug	Appropriate counselling was provided. Also, the patients and the caregivers were educated regarding the importance of medication adherence.	On follow up, 7 out of 8 patients had high medication adherence and the remaining 1 patient had low medication adherence (as per Morisky 4 medication adherence scale).

Table 3
Medication Errors and Suggestions made to solve it.

Sl. no.	Medication errors	Category	Classification	Suggested solution
1.	Five patients had taken deferasirox tablet after dissolving it in milk.	Category-D	Administration Error- Incorrect administration technique.	Advised to dissolve the deferasirox tablet in orange juice or apple juice or water for its administration.
2.	Three patients had taken deferasirox directly without dissolving the tablet in orange juice or apple juice or water.	Category-D	Administration Error- Incorrect administration technique	Advised to dissolve the deferasirox tablet in orange juice or apple juice or water for its administration.
3.	Seven patients had taken deferasirox tablet immediately after taking food.	Category-D	Administration Error- Incorrect time of administration	Advised to give deferasirox tablet half an hour before food (empty stomach).

Table 4
Assessment, classification, preventability and severity of ADRs.

ADR	Assessment	Classification	Preventability	Severity
Nausea	Probable	Type B	Definitely preventable	Level 1
Vomiting	Probable	Type B	Definitely preventable	Level 1
Dizziness	Probable	Type B	Not preventable	Level 1
Dizziness	Probable	Type B	Not preventable	Level 1
Arthralgia	Probable	Type A	Not preventable	Level 1

5. Conclusion and relevance

The prescribing patterns, DRPs and medication errors in transfusion-dependent paediatric thalassaemia patients were discussed in this study. The identified DRPs and medication errors suggest that there is a need to assess the medications in thalassaemia patients. The health care professionals should provide proper education and counselling to the patients and their caregivers regarding the importance of medication adherence in thalassaemia patients, and also about the complications related to iron overload if not managed properly.

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Ethical approval

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Declaration of competing interest

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CRediT authorship contribution statement

Tirin Babu: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **George Mathew Panachiyil:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Juny Sebastian:** Formal analysis, Writing - review & editing. **Mandyam Dhati Ravi:** Formal analysis, Writing - review & editing.

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