ORIGINAL ARTICLE

Management and Clinical Outcome of Children with Transfusion-Dependent Thalassaemia in Hospital Tuanku Ja'afar Seremban

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SUMMARY

The aim of this study was to evaluate the management and clinical outcome of transfusion-dependent thalassaemia children receiving care in the Paediatric Ambulatory Care Centre, Hospital Tuanku Ja'afar Seremban in comparison to The Malaysian Clinical Practice Guidelines. The demography, management and clinical outcome of the patients were documented using a checklist. Information on compliance to chelation agents was obtained through interview. There were twenty-six patients recruited in this study out of thirty seven patients registered in the centre. This study showed that more effort and vigilance should be given to ensure that the management of these patients adheres to the guidelines and clinical outcome of these patients monitored closely.

KEY WORDS:
Transfusion-dependent thalassaemia, children

INTRODUCTION

Children with thalassaemia major require regular blood transfusions. While hypertransfusion regime prolongs survival and reduces extramedullary haematopoiesis, it potentially leads to transfusion-related infection, progressive iron deposition and other related complications. Although iron-chelating therapy was made available to all the patients with the government subsidies, some patients' ferritin level remain suboptimal, possibly due to poor adherence to the treatment. Appropriate monitoring and management of complications is essential. The Malaysian Clinical Practice Guidelines was established in 2009 and the management of this group of patients has been streamlined as summarized in Table I.

The objective of this study is to evaluate demography, management and clinical outcome of children with transfusion-dependent thalassaemia. The management and clinical outcome aspect of this group of patients is based on the Malaysian Clinical Practice Guidelines for transfusion dependent Thalassaemia [1].

MATERIALS AND METHODS

Patients selection

All patients with transfusion dependent thalassaemia receiving care from the Paediatric Ambulatory Care Centre in 2011 were included in this study. Exclusion criteria included children who were receiving irregular transfusions due to thalassaemia intermedia, children who did not receive transfusion during the study period and children without parental consent.

Data collection and analysis

Data was collected using a checklist and information on the patients' demography, diagnosis, treatment, investigations and growth were obtained from their medical records. Information on patient-reported compliance, side effects, difficulties related to iron chelation therapy were obtained from interviewing the parents or the patients. Compliance to iron chelation therapy was assessed through direct questioning on the number of tablets or vials of iron chelator taken or used per day/ week as compared to the number prescribed to the patient. The study was commenced for duration of three months from 1 December 2011 to 31 March 2012. Data was analyzed using the SPSS version 17.

Ethics approval

Approval was obtained from the Malaysian Research Ethics Committee. Consent from the patients' parents was obtained prior to data collection.

RESULTS

During the study period, a total of 26 patients were recruited out of 37 patients registered with the Paediatric Ambulatory Care Centre of Hospital Tuanku Ja'afar Seremban. The children who were excluded from the study were six patients receiving irregular transfusions due to thalassaemia intermedia, one patient admitted to a transplant centre awaiting bone marrow transplant and four children without parental consent.

Demographic data

The demography of the children with thalassaemia is summarized in Table II. The youngest patient was 2 years old and the eldest was 15 years old. Most of the children were from Seremban district, the thalassaemia patients from the other districts mostly receive regular transfusion in the nearest hospital.

Management

Table III summarizes the findings in the management of the patients in this study. There were two patients who were

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Table I: Summary of recommendations from the Malaysian clinical practice guidelines on thalassaemia

Clinical parameter	Recommendation
Blood transfusion	o Pre-transfusion Hb 9-10g/dL o Post-transfusion Hb 13.5-15.5g/dL
Splenectomy	o Considered when a patient > 5 years old, with increased transfusion requirement >200-250 ml/kg/year pure RBC o Evidence of hypersplenism o Massive splenomegaly o Immunoprophylaxis and chemoprophylaxis must be adhered to. o Patients must be educated on the risks so that they can seek early treatment.
Assessment of iron burden	o Serum ferritin should be monitored every 3-6months. o MRI T2* should be used to assess cardiac iron status in older children. o MRI R2 can be used to assess liver iron.
Iron chelation therapy	o All patients with iron overload (Serum Ferritin [SF] >1000µg/L on 2 occasions in at least 2 weeks apart) should receive iron chelation therapy. o Aim to keep SF level near to 1000µg/L, Liver Iron Concentration<7mg Fe/g DW liver, cardiac T2* >20ms.
COMPLICATIONS	
Infection	o All patients should be tested for viral markers at diagnosis and every 6 months: o HBsAg, anti-HCV antibody, anti-HIV antibody.
Growth delay	Definition of growth failure: o Height <3rd percentile for age/gender o Significantly short for the family (10cm or more below Mid Parental Height) o Slow growth rate observed over a period of 6 months to 1 year o Downward crossing of height percentiles on growth chart Recommendation: o Thalassaemia patients with short stature should be assessed and screened for growth hormone deficiency after excluding other common causes of short stature. o Growth hormone deficiency should be confirmed by conducting 2 GH stimulation tests using 2 different pharmacologic agents. o Growth hormone therapy if required should be tried for one year and assessed for response.
Delayed puberty	Definition: o Delayed puberty: the complete lack of pubertal development by 13 years in girls, by 14 years in boys. Hypogonadism is defined in boys as the absence of testicular enlargement (<4mls), and in girls by the absence of breast development (thelarche) by 16 years. o Arrested puberty: lack of pubertal pregression over one year or more. The testicular size remains 6-8mls, breast size at Tanner stage 3. Recommendation: o Tanner staging every 6 months from 10 years of age. o Orchidomenter (Prader) should be made available for the assessment of testicular volume. o Patients with delayed puberty require screening with thyroid function test, LH, FSH, oestradiol or testosterone and bone age. Pelvic ultrasound should be done to assess ovarian & uterine size. If results are abnormal, perform gonadotropin releasing hormone (GnRH) stimulation test.
Hypothyroidism	o The treatment for hypothyroidism is L-thyroxine. o Thalassaemia patients aged more than 10 years should be monitored annually for hypothyroidism.
Diabetes Mellitus	o Symptoms + RBS>11.1mmol/L o FBS >7.0mmol/L o 2HPP >11.1mmol/L on an oGTT Impaired glucose tolerance: 2-hour postprandial blood glucose 7.8-11.1mmol/L Recommendation: o A 2-hour oGTT should be performed annually on thalassaemia patients >10 years o Thalassaemia patients with IGT should be managed by a strict diabetic diet, weight reduction where applicable and intensive iron chelation. o Thalassaemia patients with DM should be treated with insulin.
Osteoporosis/ osteopenia	Definition: o Osteopaenia: mild decrease in bone mineral content, 1.1-2.4SD below the mean for age and sex. o Osteoporosis: a decrease in bone mineral content, 2.5SD or more below the mean for age and sex, and resulting in weak bones and pathological fractures. Recommendation: o Adequate dietary intake of calcium and vitamin D should be ensured. o Regular weight-bearing exercises should be encouraged with avoidance of smoking and excessive alcohol consumption. o Vitamin D, calcium and zinc status of thalassaemia patients should be evaluated regularly and annually from 10 years old onwards. o Annual bone density studies should be considered in thalassaemia patients more than 10 years of age.
Hypoparathyroidism	o Annual screening is suggested from age of 10 years onwards. o Treatment of hypoparathyroidism consists of calcitriol with or without calcium carbonate/lactate.
Hypoadrenalism	Thalassaemia patients more than 10 years of age, especially those with wasting and other endocrinopathies should be monitored annually for hypoadrenalism.

Cardiac complication	o Annual monitoring of CVS for thalassaemia patients from age 10 onwards would include ECG, echocardiogram, and where possible MRI T2* o For asymptomatic thalassaemia patients with mild to moderate cardiac siderosis (T2* 10-20ms) and normal cardiac function, iron chelation monotherapy should be intensified or switched to combination therapy. o If MRI T2* assessment is not possible, then thalassaemia patients with poor chelation history and high risk of cardiac iron overload such as serum ferritin > 2500µg/L or poor compliance should have intensive chelation monotherapy or switched to combination therapy. o For thalassaemia patients with severe cardiac iron overload or symptomatic cardiac disease, continuous intravenous Desferrioxamine is the best treatment option. Alternatively, combination therapy can be considered.
Nutritional support	All thalassaemia patients should be given good nutritional support at an early age to minimize growth impairment. Vitamin E is useful for thalassaemia patients. Vitamin C supplementation to be given to thalassaemia patients during desferrioxamine therapy. Folic acid supplementation is useful for thalassaemia patients on low transfusion regime and those planning for pregnancy.
Counselling for bone marrow transplantation	Matched sibling donor transplantation should be offered at the earliest age possible.

Table II: Characteristics of children with transfusion-dependent thalassaemia (n=26)

General characteristics	Number	%
Age (in complete years)		
1-5	5	19.2
6-10	6	23.0
>10	15	57.8
Ethnicity		
Malay	22	84.6
Chinese	4	15.4
Gender		
Male	14	53.8
Female	12	46.2
District		
Seremban	23	88.6
Rembau	1	3.8
Tampin	1	3.8
Selangor	1	3.8

transferred to our centre without previous medical records, hence previous data such as age of diagnosis, age of first transfusion were not obtained. Majority of the children have received 6-10 years of regular transfusions (34.6%), followed by 1-5 years (26.9%) with another 30.8% of patients receiving more than 10 years of transfusion. Only one patient received regular transfusion for less than a year.

All the patients received regular transfusion with leucoreduced blood with the interval ranging from 21 days to 91 days (mean=35.3 days with SD 17.4). The patients with transfusion intervals more that 30 days were mainly patients with β-thalassaemia intermedia and HbE-β-thalassaemia with features of thalassaemia intermedia whom require regular intervals of transfusion (n=8). Excluding the patients with features of thalassaemia Intermedia, 15 (57.7%) of the patients receiving transfusion had pre transfusion Hb of less than 9mg/dL. Only 2 (7.7%) of the thalassaemia major children had the pre Hb between 9-10 mg/dL. None of the children had post transfusion Hb done as it was not a pre-requisite in our centre.

There were 21 (80.8%) patients who were above 5 years. 15 (57.7%) of these children have criteria indicating splenectomy may be required and need to be followed up closely. The indications include increased transfusion requirement and splenomegaly. One patient had splenectomy done and currently has thrombocytosis.

There were 21 patients with serum ferritin of more than 1000 µg/L despite chelation with optimum dosage. Compliance was an issue especially for the children on desferioxamine. Reasons for the non-compliance are summarized in Table IV. None of the patients had undergone other assessment of iron stores such as liver iron concentration and Magnetic Resonance Imaging (MRIT2*).

Clinical outcome

Table V summarizes the clinical outcome of our patients. There were 19 patients more than 10 years of age, therefore were screened for complications. Among the complications screened in the patients, certain areas were found to be deficit, the areas were pubertal screening and detection of pubertal delay, hypoadrenalism, referral to dietician for nutritional support and Vitamin E supplementation. For some patients who were detected to have pubertal delay and growth delay, the problem was not investigated fully and there is the need for referral to the endocrine team.

Table III: Management of thalassaemia (n=26)

Characteristics of Management	Number	%
Diagnosis		
β-thalassaemia major	9	34.6
HbE-β-thalassaemia	16	61.5
β-thalassaemia intermedia	1	3.9
Method of diagnosis		
Hb electrophoresis	25	96.2
DNA analysis	1	3.8
Age of diagnosis		
<1 year	10	38.5
1-6 years	14	53.8
unknown	2	7.7
Age of first transfusion (in complete year)		
< 1 year	9	34.6
1-6 years	16	66.6
unknown	1	3.8
Transfusion interval (days)		
<28	9	34.6
28-30	9	34.6
>30	8	30.8
Pre transfusion Hb level (mg/dL)		
<9	24	92.3
9-10	2	7.7
Volume of transfusion/year (ml/kg/year)		
<200	10	38.5
>200-250	16	61.5
Assessment of iron burden, serum ferritin (μg/L)		
<1000	5	19.2
1000-2499	7	26.9
≥2500	14	53.9
Iron chelation		
Desferrioxamine	10	38.5
Deferiprone	2	7.7
Desferrioxamine+Deferiprone	7	26.9
Deferasirox	3	11.5
None	4	15.4
Compliance to chelation		
Desferrioxamine	8 (n=17)	47.0
Deferiprone	9 (n=10)	90.0
Deferasirox	2 (n=3)	66.7

Table IV: Reasons for non compliance to chelation

Types of chelation	Reasons
Desferrioxamine	Comes home late from tuition at night
	Unwell
	Only father is able to prepare the injection, patient and mother were taught but fear the needle, miss the injection when father works outstation
	Involves in dancing activities at night
	Refuse injections
	Pain during the injection
Deferiprone	Forgets to take
Deferasirox	Do not like to take medicine everyday

Table V: Clinical outcome of transfusion-dependent thalassaemia children

Clinical Outcome		Number	%
Growth delay (n=26)	Growth chart monitoring	26	100
	Growth failure present	15	57.7
	➢ investigated	8	30.8
	➢ treated	2	7.7
Delayed puberty (n=19)	Tanner staging done	9	47.4
	Presence of delay		
	➢ detected	5	26.3
	➢ treated	2	10.5
Hypothyroidism	Investigated	19	100
	Require treatment	0	0
Diabetes mellitus	Investigated	19	100
	Require treatment	0	0
Osteoporosis/osteopenia	Investigated	19	100
	Calcium supplement given	19	100
Hypoparathyroidism	Investigated	19	100
	Require treatment	0	0
Hypoadrenalism	Investigated	0	0
	Require treatment	0	0
Cardiac complication	Investigated		
	➢ echocardiogram	19	100
Infection (n=26)	Hepatitis B vaccination	26	100
	Hepatitis B infection	0	0
	Hepatitis c infection	0	0
	HIV infection	0	0
Nutritional support n=26	Referral to dietician	2	7.7
	Vitamin C supplement	19	73.1
	Vitamin E supplement	0	0
	Folic Acid supplement	26	100
Counselling for bone marrow transplantation	Done	13	50.0
	➢ HLA typing	4	15.4
	Not done	11	42.3
	Unknown	2	7.7

Bone marrow transplant counseling was reported in 50% of the patients in which Human Leukocyte Antigen (HLA) typing was done for 4 patients. However, only one patient had HLA matched sibling but unfortunately the patient was already in the high risk category by then.

DISCUSSION

Improved transfusion therapy and the consistent use of iron chelation therapy have extended the life span of patients with thalassaemia major[2] and transfusion dependent thalassaemia. Since 2005, the Ministry of Health, Malaysia has provided chelation therapy for free to all children with transfusion dependent thalassaemia. This has succeeded in prolonging their survival. However, the risk of developing complication related to iron deposition is still present despite availability of chelation. Chelation therapies include the subcutaneous infusion of desferrioxamine, oral therapies using deferiprone and deferasirox, and combination therapy with both desferrioxamine and deferiprone. Iron overload may cause complications such as diabetes mellitus, hypothyroidism, hypogonadism, hepatic cirrhosis and cardiac involvement including arrhythmias and congestive cardiac failure. In an Italian series, adequate chelation therapy has allowed patients to survive up to 35 years of age[3].

In our centre, cardiac complications related to iron overload was monitored by using echocardiography. However, this is may be of limited value as it is documented that once changes are seen, patients may have established cardiomyopathy. Therefore, the best method to assess cardiac iron at present is using MRIT2*[4]. At present, this service is not available in our centre, hence patients would need to be referred to nearby centres offering this service.

Combination therapy of desferrioxamine and deferiprone was started with the children with high serum ferritin. However, compliance to chelation was an issue. Compliance to oral chelators was generally better as seen in other studies as well. The children on combination therapies tend to be compliant to deferiprone but non compliant to desferrioxamine[1]. This is concurrent with the estimation of 40-50% of patients were compliant to desferrioxamine in Malaysia. Previously, the non compliance to desferrioxamine was due to the exorbitant cost and the inconvenience of injecting desferrioxamine[5]. However, even though patients receive free desferrioxamine currently, the compliance has not improved as seen in this study.

Monitoring for complications of iron overload was done although there is room for improvement. Growth was mainly monitored using growth chart. However, the patients who were detected to have growth delay were not fully investigated. These patients with growth delay should be assessed further using growth velocity and subnormal sitting height. Mid parental height should be calculated for all patients. Once growth delay is detected, investigation should be commenced and appropriate treatment instituted[6]. The prevalence of growth delay in pre pubertal thalassaemic patients as reported by Hamidah *et al* was found to be 57.7%[7], thus our patients also warrants close monitoring.

Pubertal delay and hypogonadism are other endocrine complications that require further evaluation and management. There is a need to remind attending doctors to assess pubertal development as this group of children may have delayed puberty, slow progressing puberty or arrested puberty. Appropriate treatment should be instituted after full investigation. Referral to the endocrine unit may be imperative [5].

None of the children with transfusion dependent thalassaemia were detected to have other endocrine related complication such as hypothyroidism, diabetes mellitus, hypoparathyroidism or blood borne infection. This is comparable to findings in North America [8].

Therefore, comparing our clinical practice to the recommendations in Clinical Practice Guidelines, shortcomings especially in monitoring the complications related to iron chelation therapy were identified. There is a lack of monitoring and action taken for growth delay, pubertal development, hypoadrenalism and cardiac complications. It was also noted that majority of the patients were not given appropriate dietary counseling as well as information on bone marrow transplantation as per recommendation in the Clinical Practice Guidelines.

Remedial measures

Upon evaluating the findings of the study, remedial measures have been done. Thalassaemia camp and awareness programs were held for the thalassaemia children to promote awareness and independence to their illness and management. A separate dialogue session was held for parents to meet the doctors and nurses. The use of a checklist to review management and complication is made available in the notes (Appendix A).

Limitation of the study

The limitation of this study include the small number of patients from one centre in this study may not be reflective of thalassaemia patients in the state. A bigger study for all patients in the state may be more reflective.

CONCLUSION

There is room for improvement in ensuring the transfusion-dependent thalassaemia children receive optimum management and monitoring of clinical outcome based on the Clinical Practice Guidelines available in Malaysia.

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