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Current Trends in the Management of Beta Thalassemia

A.P. Dubey, A. Parakh and S. Dublish

Department of Pediatrics, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India

ABSTRACT

The management of Beta Thalassemia, the commonest form of hemolytic anemia in children, has changed significantly in the last few years. With the availability of better transfusion regimen, iron chelation therapy, proper management of complications and good supportive care, it is now possible for a thalassemic child to have a near normal life span with a good quality of life.
[Indian J Pediatr 2008; 75 (7) : 739-743] *E-mail: apdubey52@rediffmail.com*

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As the life expectancy of children with Thalassemia Major (TM) is increasing by transfusion and chelation therapy, chronic complications are gaining more importance thus impairing the quality of life.[1,2] Hence, management of TM requires comprehensive care provided in a dedicated thalassemia unit.

A pediatric hematologist, specially trained in thalassemia care, supervises all aspects of care with other specialists including a nurse specialist, cardiologist, endocrinologist, reproduction endocrinologist, gynecologist, psychiatrist/psychologist, social worker, hepatologist and a transplant specialist.[3] This review briefly describes currents trends in the management of TM with emphasis on recent advancements.

TRANSFUSION THERAPY

Regular lifelong blood transfusions are indicated in children with a confirmed diagnosis of TM with either (a) hemoglobin <7 gm/dL or (b) morphological changes, poor growth, fractures or extramedullary hematopoiesis. This promotes normal growth and physical activity, suppresses erythropoiesis, and prevents chronic hypoxia and early splenomegaly/hypersplenism. Prior to starting transfusions extended red cell phenotyping, liver function tests, HbsAg, IgG-Anti-HCV and HIV should be done. All children should be immunized for hepatitis B.

Leucoreduced ($\leq 1 \times 10^6$), ABO and Rh compatible (if possible for C, E and Kell also) packed red cells are recommended for reducing adverse reactions [febrile non-hemolytic transfusion reactions (FNHTR)] secondary to contaminating white cells and preventing platelet alloimmunization. Leucoreduction is usually done in Indian set up by bedside filters, which removes white cells to the extent of 99.9 %. Prestorage filtration should be considered for those developing FNHTR even after the use of filters.

Duration between transfusions is 2-6 weeks depending on the weight, age, work and school schedules. Also to avoid wastage interval is adjusted to allow transfusion of a whole unit. The volume of transfused blood depends on the anticoagulant used in the particular blood bank and hence the approximate hematocrit of transfused red cells and the amount by which the hemoglobin needs to be raised. Blood is transfused at the rate of 5 mL/kg/hr, reducing to 2 mL/kg/hr in case of cardiac disease.

Pre transfusion Hb is monitored routinely to maintain an optimal pre-transfusion hemoglobin (Hb) of 9-10.5 gm/dL; patients with cardiac involvement require a higher level. Routine monitoring of post transfusion Hb is not necessary except in cases of unexplained high transfusion requirements to be maintained at 14-15 gm/dL. The best indicator of appropriate management is annual pure red cell consumption (APRCC), which would help in calculating the transfusional iron load per kg and helpful in identifying hypersplenism (if APRCC > 200 mL/kg/yr). All children should be monitored for early and delayed transfusion reactions.[2]

IRON OVERLOAD

It is estimated that with regular blood transfusion therapy (approximately 100-200 ml/kg/year of pure red cells) 0.32-0.64 mg/kg/day of iron is added to the body. Also

Correspondence and Reprint requests : Dr. A.P.Dubey, Professor and Head, Department of Pediatrics, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi-110002.

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gut iron absorption increases in poorly transfused patients, adding to the iron load. Most of the chronic complications in TM are caused by iron induced cell damage. Hence, chelation therapy in TM is the other most important treatment after blood transfusion.[2]

Iron overload can be measured by either serum ferritin estimation or by liver iron content (LIC). Serum Ferritin estimation is easy, inexpensive, can be repeated frequently and correlate with morbidity and mortality although it is known to fluctuate with inflammatory and infectious conditions. If followed serially over time and certain drawbacks recognized, it still seems to be the most widely used, most acceptable and feasible investigation in resource-limited settings. Measurement of LIC by liver biopsy is the validated reference standard and measures LIC directly, but it is invasive and facilities for LIC estimation on the biopsy samples are not widely available. LIC should be considered in those patients with coexisting hepatitis, uncertain chelation responses or when new chelation regimens are used. LIC can also be measured by SQUID but rarely available and hence impractical or R2 spin Echo MRI of the liver, which is an upcoming technique.

CHELATION THERAPY

Chelation therapy is usually started after 10-20 transfusions or when serum ferritin level reaches >1000 g/l. Comparison of different iron chelators is shown in table 2.

Desferrioxamine (DFO) : Since 1963 DFO has remained the "gold standard" iron chelator. When administered in adequate doses it reduces iron overload, improves cardiac function and has been shown to reduce iron-related morbidity and mortality.[4] Unfortunately, compliance still remains a serious limiting factor in treatment success because of requirement of subcutaneous infusions and high cost. Vitamin C has been shown to increase the availability of cheatable iron and is given at the time of desferrioxamine infusion in the dose of 2-3 mg/kg/day. In cases of severely overloaded patients and those with significant cardiac disease [significant cardiac dysrhythmias, evidence of failing left ventricular function, evidence of very severe heart iron loading (T2*<6 ms)] 24-hour intensive therapy with continuous infusion using a port-a-cath is recommended.

Deferiprone : It is the second iron chelator introduced in March 1995 and extensively used in India. Although the efficacy is lower as compared to DFO, the advantages include that it can be used orally and it is cheaper as compared to DFO. Some studies have also shown that it chelates cardiac iron better.[5] It has limiting adverse effects such as arthropathy and neutropenia.

***Deferasirox* :** Deferasirox is a new tridentate oral iron chelator approved by FDA for children above 2 years and is now available in India since April 2008. Deferasirox has demonstrated safety and efficacy in large multi-centric clinical phase II trials[6-9] and III trials[10] and was non-inferior to DFO with no major adverse effects. The benefit to risk profile of deferasirox is favorable. The cost effectiveness was favorable in costing models. This promising new oral drug will decrease the burden of subcutaneous or intravenous infusion, which might improve compliance and hence the life expectation.

Combined chelation : Combined chelation offers several advantages such as access to different iron pools, prevention of non-transferrin bound iron accumulation, increased efficacy, reduced toxicity and better

Table 1. Monitoring Protocol for Children with Thalassemia Major

	Which Test	When to monitor
General	Weight, Height, SMR Staging, Liver/ spleen size	6 Monthly
	HbsAg, Anti- HCV, HIV	Yearly
Blood transfusion record analysis	Annual Pure Red Cell Consumption (ml/kg/year)	Yearly
Cardiac Evaluation	ECG and HOLTER	Every 2 y till age of 12 y, then yearly or as clinically indicated
	ECHO	For <12y every alternate year. For >12y yearly. Asymptomatic patients with moderate cardiac impairment evaluate 6-8 monthly. Severe impairment every 1-4 months
	Cardiac MRI	No clear recommendation
Dental Evaluation	Caries,	Yearly
Pulmonary Function Tests	Spirometry, lung volumes, diffusion capacity	No Clear Recommendations
Endocrine evaluation		
Thyroid	FT4, TSH, if low then -TRH test with TSH response and bone Age	Yearly from 12 years
Pancreas	Glucose tolerance test	Yearly from the age of puberty
Parathyroid	Serum calcium, phosphate, if abnormal then parathormone level	Yearly from the age of 16 years

Table 2. Comparison of Various Iron Chelators

1. Desferrioxamine	
Dose	20-40 mg/kg as subcutaneous nighttime infusion over 8-10 hours of 10% solution 5-7 nights /week. Not to exceed 40 mg/kg until growth has ceased. Maximum 50-60 mg/kg
Toxicity	Local skin reactions at infusion sites, auditory and retinal toxicity, skeletal changes, growth retardation
Monitoring	***3 Monthly-*** Mean daily doses, Ferritin, Creatinine, *Therapeutic Index, Compliance index. ***Yearly-*** Color vision, Cataract, Visual fields, Fundus, Audiometery, Skeletal Changes, Sitting/Standing height, Height velocity
2. Deferiprone	
Dose	50-100 mg/kg /day orally in 2-3 divided doses
Toxicity	Common abdominal discomfort; arthropathy. Rare severe agranulocytosis (1%)
Monitoring	***Every Visit-*** Total and differential counts, joints complaints (Joint stiffness, arthralgia, effusion), Other adverse events (Abdominal discomfort, bowel upset) ***3 Monthly-*** Dose, Ferritin, ALT
3. Deferasirox	
Dose	20 mg/kg orally once daily as a single daily dose; adjust dose in increments of 5 or 10 mg/kg every 3-6 m based on ferritin trends with maximum of 30 mg/kg/day
Toxicity	Transient gastrointestinal events; skin rash; mild increased creatinine (clinically insignificant)
Monitoring	***Monthly-*** renal and hepatic function ***Yearly-*** Color vision, Cataract, Visual fields, Fundus, Audiometery.

***Therapeutic Index-** mean daily dose in (mg/kg)/ Serum ferritin (aim is to keep <0.025), **Mean daily dose –** actual dose received on each occasion X doses per week/7, **Compliance index-** number of days of treatment per year/ Number of days for which treatment is prescribed

compliance. Sequential therapy with daily deferiprone and twice-weekly DFO has been used by many authors and shown to be better or equal to 5 days a week DFO therapy.[11]

The Thalassemia International Federation recommends starting chelation with DFO or Deferasirox at standard doses as first line therapy. In case of non-improvement dose is hiked to maximum doses gradually. The chelators are switched in case of no significant response to increased dose. In case of no significant response combination therapy can be considered. In case of intolerance to the drug the chelator can switch immediately. Deferiprone can be used as a monotherapy if this switch is ineffective and other chelator cannot be used.

CARDIAC COMPLICATIONS

Cardiac dysfunction is the most common cause of death in patients with TM.[1] The reported incidence of cardiac dysfunction and heart failure varies widely (from 3% to 37%) due to highly variable age distribution and treatment cohorts. The mechanism of heart injury includes iron overload, chronic anemia, vascular damage, increased pulmonary vascular resistance, infections and endocrinopathies such as hypothyroidism, diabetes and hypoparathyroidism. Vitamin C can precipitate cardiac failure by release of excess free iron.

Heart failure can present at any time after the age of 10 yrs but with optimal treatment, heart failure usually occurs in the third or fourth decade of life. TM patients with signs and symptoms of CCF should be hospitalized and closely monitored. Laboratory tests such as arterial blood gas, endocrine profile, liver and renal function tests, chest X-ray, ECG, doppler echocardiographic study and MRI measurements—to determine the degree of iron overload should be done as per feasibility. Triggering factors for CCF (arrhythmias, blood volume overload after transfusion, infections, and severe anemia) should be identified and treated. The essential intervention is intensification of chelation therapy; combination of the two iron chelators (DFO and deferiprone) maximizes the efficacy.[12] If deferiprone is contraindicated, continuous desferrioxamine infusions should be used, requiring the placement of an indwelling catheter. Transfusions are given to maintain hemoglobin above 10 g/dL. Endocrinopathies should be managed. Diuretics—loop diuretics, potassium-sparing agents and ACE inhibitors should be prescribed. Digoxin is prescribed to patients with atrial fibrillation resistant to conversion.

ENDOCRINE COMPLICATIONS

Patterns of growth are relatively normal until the age of 9-10 years when growth velocity begins to slow. The etiology of growth failure in Thalassemic children is multifactorial and includes chronic anemia, hypersplenism, chronic liver disease (HBV, HCV), Zinc and Folic acid deficiency, skeletal dysplasia, Desferrioxamine toxicity, and emotional disturbance. endocrinopathies such as hypothyroidism, delayed puberty, hypogonadism, dysfunction of the growth hormone insuline - like growth factor - 1 (IGF 1) axis are also contributory.[13-15] Approach to a stunted child with thalassemia is similar to a stunted child without thalassemia.

Hypothalamic – Pituitary – Gonadal Axis : Iron deposition

in the pituitary gonadotroph cell is the underlying mechanism of panhypopitutarism leading to hypogonadotrophic hypogonadism and delayed puberty. Hypergonadotrophic hypogonadism is rare. Pituitary GH deficiency, GH resistance, and GH neurosecretory dysfunction are known to occur.

Hypothyroidism : This complication is relatively rare and presents in the second decade with primary type being commoner than secondary. Typically, there is no thyromegaly and thyroid antibodies are negative. It can range from sub-clinical to mild to overt disease. Treatment is with L-thyroxine.

Hypoparathyroidism : This rare complication, presents after the age of 16 years with mild hypocalcaemia and very rarely with tetany and cardiac failure. The diagnosis is based on low serum calcium, high phosphate and low PTH levels. The oral administration of Vitamin D and calcium is the treatment of choice, with frequent monitoring of serum and urine calcium levels.

Diabetes Mellitus : It is seen after the age of 10 years. The etiology is multifuctorial and includes Beta cell destruction due to iron overload, chronic liver disease, hormonal treatment and genetic factors. The pathogenesis resembles type-2 diabetes, with children presenting in the early second decade of life. The spectrum varies from impaired fasting intolerance to impaired glucose intolerance to overt diabetes. The patients are advised to follow a proper diet, lose weight and intensify chelation. Oral hypoglycemic drugs such as Metformin and Glibenclamide are given when indicated. Insulin therapy is considered in the stage of insulin deficiency, where all other measures fail.[16-17]

The prevention of growth retardation is essential. Growth monitoring should be done in all children by using growth charts (both distance and velocity charts) [WHO growth charts are now available up to 19 years and can be used, Tanner growth velocity charts for height velocity] for both standing and sitting height. The mean hemoglobin levels must be kept near 10g/dl, before transfusion and the dose of desferrioxamine should be 35 mg/Kg for children to avoid its toxic effect on bones. Prompt initiation of iron chelation therapy prevents pituitary haemosiderosis, which is the main cause of GH insufficiency. Therapeutic response with GH administration in cases with GH deficiency, is often satisfactory. Growth acceleration is mostly promoted with sex steroids in children with pubertal delay.

INFECTIONS

Infections are major complications and constitute the second most common cause of death and a main cause of morbidity in patients with TM. Predisposing factors include severe anemia, iron overload, splenectomy, and a range of immune abnormalities. Major causative organisms of bacterial infections in TM patients are *Klebsiella* spp and *Yersinia enterocolitica.* Transfusion-associated viral infections (especially hepatitis B and C) can lead to cirrhosis and hepatocellula\r carcinoma.[18]

MENTAL HEALTH

Chronic illness affects psychological health and self esteem in children. Hence, in addition to the physical aspects it is necessary also, to focus on the psychological health of the child in order to ensure compliance and thus treat the child comprehensively. The prevalence of psychological problems in children with TM has been reported to be 43-44%. Anxiety and related problems, emotional problems, particularly depression, somatization and conduct problems are the main findings.[19-20] The chronic illnesses like TM impose persistent stress on the caregivers too. Psychiatric problems, especially depressive disorders are quite common. The greatest concerns are regarding the future, illness and finances. Therefore, caregiver support through psychological interventions or medication is important for a better quality of life.[20]

FERTILITY AND REPRODUCTION

With significantly increased average lifespan and improved quality of life in patients with TM, attainment of reproductive capacity and creation of a family has become a great task. Early recognition and treatment of endocrinopathies is very important to prevent late complications and increase the chances of parenthood. The reports of successful pregnancies provided strong evidence not only for the absence of any deleterious effect on the course of TM but also for the safety of the pregnancy in the TM woman. Spontaneous pregnancies in women with preserved Hypothalamic – Pituitary – Gonadal axis, who has normal menstrual cycles, are common. Ovarian function is well preserved in women suffering amenorrhea as they become able to conceive following a closely monitored stimulation therapy. Males who have normal gonadal function maintain their spermatogenic ability and therefore, frequently become fathers. On the other side of the spectrum, in cases where impaired spermatogenesis is present, a combination treatment with gonadotrophins has proved to be beneficial in improving their reproductive capacity.[21-26]

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