

Original Article

Effect of Long Term Desferrioxamine Treatment on Final Height in Children with Transfusion Dependent Thalassemia

Bunchoo Pongtanakul, Patsarapon Wongthawatchai, Nassawee Vathana and Nattee Narkbunnam

Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University

Abstract:

Background: Thalassemia is the most common hereditary anemia. Desferrioxamine (DFO) is the iron chelator. One of the side effects is the impact on growth when used long term and starting since young age. **Objective:** The study aimed to determine the effect of long term DFO treatment on height in childhood transfusion dependent thalassemia (TDT). **Materials and Methods:** We retrospectively reviewed patients' charts between 5 to 15 years old with TDT who received DFO for more than 5 years from 2006-2010. **Results:** Fifty-two patients were enrolled; median age at start of DFO was 5.3 (1.6-12.2) years and duration of DFO treatment was 9.2 ± 2.8 years. Mean DFO dosage was 30.8 ± 8.8 mg/kg/day and mean pretransfusion hemoglobin was 10.4 ± 1.2 g/dL. We compared between heights of TDT before and after DFO using height percentile and Z-score. In all, 40 patients (77%) decreased while 11 patients (21%) increased in height percentile and only one patient (2%) had stable height percentile. The mean difference of height percentile between before and after DFO treatment was -18.8 ± 28.1 which showed the height percentile after DFO treatment was significantly lower than before DFO ($p < 0.001$). When we analyzed using height Z-scores, 38 patients (73%) decreased height Z-scores while 10 (19%) and 4 patients (8%) increased and presented stable height Z-scores. The mean difference of height Z-scores between before and after DFO was -0.33 ± 0.50 indicating post DFO treatment score was significantly lower than pre DFO treatment ($p < 0.001$). **Conclusion:** Long term DFO treatment in childhood TDT receiving hypertransfusion can impair final height.

Keywords : ● Transfusion dependent thalassemia ● Desferrioxamine ● Final height

J Hematol Transfus Med 2017;27:145-50.

Received 26 November 2016 Accepted 8 February 2017

Correspondence should be addressed to Assoc. Prof. Bunchoo Pongtanakul, MD., Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700 Email: bunchoo.pon@mahidol.ac.th

Original Article

Effect of Long Term Desferrioxamine Treatment on Final Height in Children with Transfusion Dependent Thalassemia

บุญชู พงศ์ธนากุล ภัสราพร ว่องวัชชัย ณัฏวีร์ วัฒนา และ นัทธี นาคบุญนำ
สาขาวิชาโลหิตวิทยาและอองโคโลยี ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

ความเป็นมา Desferrioxamine (DFO) มีผลข้างเคียงคือ การเจริญเติบโตผิดปกติเมื่อใช้ยาในระยะเวลาสั้นและเริ่มใช้ยาเมื่ออายุน้อย **วัตถุประสงค์** เพื่อศึกษาผลของ DFO ระยะยาวต่อส่วนสูงของผู้ป่วยธาลัสซีเมียชนิดพึ่งพาเลือด (TDT) **วัสดุและวิธีการ** ทำการศึกษาโดยการทบทวนเวชระเบียนย้อนหลังใน TDT ที่ได้รับเลือดสม่ำเสมอ และได้รับยา DFO ต่อเนื่องเป็นเวลานานอย่างน้อย 5 ปี ระหว่างปี พ.ศ.2549-2553 **ผลการวิจัย** มีผู้เข้าร่วมการศึกษา 52 ราย ค่ามัธยฐานอายุที่เริ่มยา DFO 5.3 (1.6-12.2) ปี ระยะเวลาที่ได้รับยา 9.2 ± 2.8 ปี ขนาดยาเฉลี่ย 30.8 ± 8.8 mg/kg/day ระดับฮีโมโกลบินเฉลี่ยก่อนได้รับเลือด 10.4 ± 1.2 g/dL เมื่อเปรียบเทียบความสูงโดยใช้ height percentile ก่อนและหลังได้รับยา DFO พบว่า มีผู้ป่วย 40 ราย (ร้อยละ 77) มี height percentile ลดลง 11 ราย (ร้อยละ 21) เพิ่มขึ้น และ 1 ราย (ร้อยละ 2) คงที่ ค่าเฉลี่ยความแตกต่างของ height percentile ก่อนและหลังได้รับ DFO คือ -18.8 ± 28.1 แสดงว่า เมื่อใช้ height percentile ผู้ป่วยมีส่วนสูงลดลงหลังได้ DFO อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) เมื่อใช้ height Z-scores มีผู้ป่วย 38 ราย (ร้อยละ 73) มี height Z-scores ลดลง 10 ราย (ร้อยละ 19) เพิ่มขึ้น และ 4 ราย (ร้อยละ 8) คงที่ ค่าเฉลี่ยความแตกต่างของ height Z-scores ก่อนและหลังได้รับ DFO คือ -0.33 ± 0.50 แสดงว่า เมื่อใช้ height z-scores ผู้ป่วยมีส่วนสูงลดลงหลังได้ DFO อย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) **สรุป** ผู้ป่วยเด็ก TDT มีส่วนสูงสุดท้ายตามเกณฑ์ลดลงเมื่อได้รับยาขับเหล็ก DFO ระยะยาว

คำสำคัญ : ● Transfusion dependent thalassemia ● Desferrioxamine ● Final height

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต 2560;27:145-50.

Introduction

Thalassemia is the most common hereditary anemia in Thailand. The mainstay treatment for transfusion dependent thalassemia (TDT) includes regular blood transfusion. Iron overload is the main complication in TDT. Desferrioxamine (DFO) is one of iron chelators used to treat transfusion related chronic iron overload. One of the toxic features of DFO is the bony change associated with the induction of metaphyseal lesions and long bone dysplasia^{1,2}. The risk is increased when high doses of DFO therapy are initiated at an early age¹. The aim of this study was to determine the effect of long term DFO treatment on final height among Thai children with TDT.

Materials and Methods

We conducted a retrospective chart review among children treated at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital from 1 January 2006 to 31 December 2010. The inclusion criteria consisted of children with TDT aged between 5 and 15 years who had been treated with regular blood transfusion regimen and received long term DFO subcutaneously for at least 5 years. We excluded patients who had underlying diseases that may have affected the growth and height such as congenital heart disease, metabolic syndrome, immune deficiency, chronic respiratory disease, malnutrition and genetic syndromes. We recorded the height, weight, age and dosage of DFO at the start of iron chelation and serially measured their height and weight until they reached final height or DFO was switched or combined with other iron chelators. The height and weight were presented as percentile and calculated to Z-scores using the national growth references for Thai children under 20 years of age, version 1999, by the Nutrition Division, Department of Health, Ministry of Public Health, Thailand. Duration and dosage of DFO were recorded. Serial serum ferritin (SF) was measured to determine iron overload status during DFO usage. Visual examination and audiogram were monitored yearly during

DFO treatment. The percentiles, Z-scores of height and weight and SF were compared using paired t-test. The study was approved for human research ethics by The Siriraj Institutional Review Board (SIRB).

Results

Fifty-two patients meeting the inclusion criteria were enrolled in this study. Thirty-eight patients had β thalassemia/HbE, 13 patients had β thalassemia major and 1 patient had survived Bart's hydrops fetalis (22 males and 30 females). The demographic data of patients are shown in Table 1. Patients had pretransfusion hemoglobin levels of 10.4 ± 1.2 g/dL. Therefore, they received adequate regular blood transfusion. Regarding DFO usage, median age at the start of DFO was 5.3 (1.6-12.2) years. Mean dosage of DFO was 30.8 ± 8.8 mg/kg/day, at the recommended dosage and mean duration of DFO usage was 9.2 ± 2.8 years. However, SF level after DFO use was higher than SF level before DFO use implying that they might have inadequate iron chelation.

Regarding height and weight measured by percentile before and after DFO treatment, 40 patients (76.9%) had decreased their height percentile, while 11 (21.1%) and 1 (2%) patients had increased or maintained their height percentile after DFO treatment, respectively. Both height and weight percentile decreased significantly after DFO treatment (p-value < 0.001 and 0.003, respectively). For height and weight measured by Z-scores before and after DFO treatment, 38 patients (73%) had decreased their height Z-scores, while 10 (19%) and 4 (7%) patients had increased or maintained their height Z-scores after DFO treatment. The height Z-scores decreased significantly after DFO treatment (p-value < 0.001). The weight Z-scores also decreased after DFO treatment but not significantly (p-value = 0.134). The height and weight measured by percentile and Z-scores before and after DFO treatment are shown in Table 2. This indicated that most patients had decreased their growth velocity after DFO treatment.

We divided our enrolled patients in 2 groups. Group 1 comprised TDT patients whose height percentile or

Table 1 Demographic data

		Range
Gender		
Male	22 (42.3%)	
Female	30 (57.7%)	
Diagnosis		
β Thalassemia/Hb E disease	38 (73.1%)	
β Thalassemia major	13 (25%)	
Bart's hydrops fetalis	1 (1.9%)	
Median age at start DFO (year)	5.3	1.6-12.2
Duration of DFO usage (years)	9.2 ± 2.8	5.0-17.7
Maximum dosage of DFO (mg/kg/day)	30.8 ± 8.8	15.1-60.0
Pre-transfusion hemoglobin (g/dL)	10.4 ± 1.2	7.4-13.5
Serum ferritin (ng/mL)		
Before DFO*	2,940.4 ± 1,662.18	1,042-8,870
After DFO (end of study)*	4,949.6 ± 3,281.9	812-17,783

DFO, Desferrioxamine; Values, Mean ± SD; *p-value < 0.001

Table 2 Height and weight before and after desferrioxamine (DFO)

	Before DFO	After DFO	Difference before-after DFO	p-value
	Mean ± SD (min, max)	Mean ± SD (min, max)	Mean ± SD (min, max)	
Height (percentile)	48.5 ± 24.6 (3, 97)	29.7 ± 27.5 (2, 97)	-18.8 ± 28.1 (-92, 56)	< 0.001
Weight (percentile)	47.6 ± 22.0 (10, 98)	37.9 ± 26.5 (2, 98)	-9.7 ± 22.2 (-56, 37)	0.003
Height (Z-scores)	0.04 ± 0.34 (-0.7, 0.7)	-0.37 ± 0.53 (-1.6, 0.8)	-0.33 ± 0.5 (-0.47, -0.19)	< 0.001
Weight (Z-scores)	-0.10 ± 1.10 (-1.8, 3.5)	-0.48 ± 2.03 (-3.3, 10.8)	-0.33 ± 0.5 (-0.47, -0.19)	0.134

Table 3 Comparison between serum ferritin and thalassemia patients' height change after desferrioxamine (DFO) treatment

Serum ferritin (ng/mL)	Before DFO (mean ± SD)	After DFO (mean ± SD)	Difference before-after DFO (mean ± SD)	p-value
Group 1 (percentile)	3,009.3 ± 1,790.7	5,21.5 ± 3,641.2*	2,712.2 ± 3,576.7	0.001
Group 2 (percentile)	2,710 ± 1,168.7	4,376.6 ± 1,570.7*	1,666.1 ± 1,884.9	0.011
Group 1 (Z-scores)	2,984.2 ± 1,787.4	5,129.8 ± 3,689.4 [#]	2,145.7 ± 3,611.1	0.001
Group 2 (Z-scores)	2,821.5 ± 1,313.3	4,460.4 ± 1,778.3 [#]	1,638.9 ± 2,051.8	0.010

Group 1: Thalassemia patients who decreased their height after DFO

Group 2: Thalassemia patients who increased or stable their height after DFO

*p-value = 0.681; [#]p-value = 0.623

Z-scores after DFO treatment decreased and group 2 comprised TDT patients whose height percentile or Z-scores after DFO treatment increased or stabilized. Table 3 shows comparison serum ferritin (SF) levels between before and after DFO treatment in each group. We compared SF level using height percentile; mean SF level in group 1 before and after DFO treatment was $3,009.3 \pm 1,790.7$ ng/mL and $5,121.5 \pm 3,641.2$ ng/mL, respectively. In group 1, SF level after DFO treatment was significantly higher than before DFO treatment (p -value = 0.001). Mean SF level in group 2 before and after DFO treatment was $2,710.5 \pm 1,168.7$ ng/mL and $4,376.6 \pm 1,570.7$ ng/mL, respectively. In group 2, SF level after DFO treatment was also significantly higher than before DFO treatment (p -value = 0.011). However, when we compared mean SF level after DFO between groups 1 and 2, no statistical significance was observed (p -value = 0.681).

When we compared SF level using height Z-scores; mean SF level before and after DFO treatment in group 1 was $2,984.2 \pm 1,787.4$ ng/mL and $5,129.8 \pm 3,689.4$ ng/mL, respectively. In group 1, SF level after DFO treatment was significantly higher than before DFO treatment (p -value = 0.001). In group 2, mean SF level before and after DFO treatment was $2,821.5 \pm 1,313.3$ ng/mL and $4,460.4 \pm 1,778.3$ ng/mL, respectively. In group 2, SF level after DFO treatment was also significantly higher than before DFO treatment (p -value = 0.010). However, when we compared mean SF after DFO between groups 1 and 2, no significant difference was found (p -value = 0.623). Other severe side effects of DFO such as visual or auditory abnormality were not found in this study.

Discussion

The improvement in survival and quality of life of TDT can be achieved by regular blood transfusion, availability and adequacy of iron chelation³. The effects on linear growth and development among thalassemia patients under different blood transfusion regimens have been reported. Normal linear growth has been shown

among patients with TDT who underwent hypertransfusion regimen; this treatment can contribute to normal growth during the first ten-year of life⁴. Our study enrolled 52 patients with TDT who underwent hypertransfusion regimen with pretransfusion hemoglobin level of 10.4 ± 1.2 g/dL meaning that they received adequate and regular blood transfusion.

DFO is one of the iron chelators which has been the standard treatment for TDT with transfusion related hemochromatosis for the past 40 years⁵⁻⁶. DFO effectively maintains near normal iron balance, reduces iron overloaded organ damage and also increases life expectancy among patients with TDT⁷. Dose-related side effects include auditory problems, growth retardation and retinal toxicity which can occur among patients who are not severe iron overloaded and who receive a high dosage of DFO⁸. One of the serious complications of DFO is growth retardation. De Virgiliis S, et al.¹ studied patients with thalassemia major (mean age of 8 ± 6 months) who received regular blood transfusion and DFO administered subcutaneously daily at the dose 50-80 mg/kg/day at the same time of starting regular blood transfusion. The study showed that these patients had more markedly stunted growth and presented a clinical and radiologic rickets-like syndrome associated with joint stiffness when compared with patients with thalassemia major who received the same regular blood transfusion regimen but initiated DFO subcutaneous treatment after the age of 3 years with the same dosage. Olivieri NF, et al.² also reported marked abnormality of the metaphyseal growth plate in the distal ulnar, radial and tibial metaphyses and also a significant decline in mean height percentile among 11 of 37 children with homozygous β thalassemia who initiated DFO subcutaneously at the age less than 7 years for more than 36 months. Moreover, only patients who started DFO before the age of 2 years showed a significant decline in height percentile by the third year when compared with patients who began DFO after the age of 5 years. Our study demonstrated that 76.9% and 73% of our patients had significantly decreased their height

percentile and height Z-scores (p value < 0.001). Our patients started DFO at the median age of 5.3 (1.6-12.2) years which does not constitute an extremely young age as previously reported. The mean dosage of DFO was 30.8 ± 8.8 mg/kg/day, which was at the recommended dosage and mean duration of DFO usage was 9.2 ± 2.8 years, which is long enough to cause growth decline.

The major obstacle of DFO for achieving optimal iron balance is compliance including inconvenience, pain and the complexity and discomfort of DFO administration⁹. In Thailand, Kusuwan T, et al.¹⁰ studied 120 Thai patients with β thalassemia who had been receiving DFO subcutaneously for more than 2 years (maximum of 12 years) and showed that only 14% of cases could be classified as having good compliance. In Malaysia¹¹, the prevalence of growth retardation (such as growth velocity less than percentile) among patients with β thalassemia or β thalassemia/HbE, who were transfusion dependent and aged 2-13 years, was 57.7%. The mean SF level of the patients with a height less than one third percentile was significantly higher than patients with a height more than one third percentile. Inadequate iron chelation and compliance with iron chelator were the main problems. Our study demonstrated that SF level after DFO treatment was higher than SF before DFO treatment in both patients with TDT in whom their height percentile and height Z-scores decreased and those in whom their height percentile and height Z-scores increased or stabilized. That means inadequate iron chelation treatment with DFO was the main concern among our patients. This problem may have contributed to growth impairment in our patients. Delayed puberty and growth retardation are common in adolescent thalassaemia patients and the cause could be due to iron overload or the toxic effects of DFO. Multiple endocrinopathies including hypogonadism, hypothyroidism and diabetes mellitus occur mainly among thalassemia patients who have high SF levels¹². However, some patients with TDT in our study with inadequate iron chelation had their height percentile and height Z-scores increased or stabilized. This study

demonstrated the importance of growth monitoring among patients with TDT receiving regular transfusion and DFO treatment as iron chelation therapy.

Summary

Children with TDT receiving hypertransfusion and treated with DFO as iron chelator can experience growth impairment. Height monitoring during childhood TDT during DFO treatment is highly recommended.

References

1. De Virgiliis S, Congia M, Frau F, Argioli F, Diana G, Cucca F, et al. Deferoxamine-induced growth retardation in patients with thalassemia major. *J Pediatr*. 1988;113:661-9.
2. Olivieri NF, Koren G, Harris J, Khattak S, Freedman MH, Templeton DM, et al. Growth failure and bony changes induced by deferoxamine. *Am J Pediatr Hematol Oncol*. 1992;14:48-56.
3. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*. 2004;89:1187-93.
4. Viprakasit V, Tanphaichitr VS, Mahasandana C, Assteerawatt A, Suwanto L, Veerakul G, et al. Linear growth in homozygous beta-thalassemia and beta-thalassemia/hemoglobin E patients under different treatment regimens. *J Med Assoc Thai*. 2001;84:929-41.
5. Coa A, Gabutti V, Galanello R, Masera G, Modell B, Plama A. Management protocol for the treatment of thalassemia patients. *Nicisia: Thalassemia international federation*. 1997:32.
6. Cohen AR. New advances in iron chelation therapy. *Hematology American Society of Hematology Education Program*. 2006:42-7.
7. Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E. Thalassemia. *Hematology American Society of Hematology Education Program*. 2004:14-34.
8. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood*. 1997;89:739-61.
9. Viprakasit V, Lee-Lee C, Chong QT, Lin KH, Khuhapinant A. Iron chelation therapy in the management of thalassemia: The Asian perspectives. *Int J Hematol*. 2009;90:435-45.
10. Kusuwan T, Pangnukroh L, Leekamnerdthai W, Sangpraypan T, Viprakasit V. Analysis of treatment compliance and related health and social determining factors in Thai thalassemia patients under long-term deferrioxamine administration. *Siriraj Nursing J*. 2008;2:2-14.
11. Hamidah A, Arini MI, Zarina AL, Zulkifli SZ, Jamal R. Growth velocity in transfusion dependent prepubertal thalassemia patients: Results from a thalassemia center in Malaysia. *Southeast Asian J Trop Med Public Health*. 2008;39:900-5.
12. Low LC. Growth, puberty and endocrine function in beta-thalassaemia major. *J Pediatr Endocrinol Metab*. 1997;10:175-84.