EFFECT OF DIFFERENT TRANSFUSION REGIMENS ON CRANIOFACIAL APPEARANCE AND DENTITION IN SEVERE THALASSEMIC CHILDREN

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Abstract. Thalassemia is a group of inherited diseases with a defect in the synthesis of hemoglobin. Severe thalassemic subjects suffer from craniofacial deformities and malocclusion due to bone marrow hyperplasia compensating for ineffective erythropoiesis. Blood transfusions are used to maintain life and reduce complications. The transfusions may have benefits in reducing craniofacial and dentition abnormalities. However, appropriate therapy is still controversial. This study evaluated the effect of different transfusion regimens on craniofacial appearance and dentition. Ninety-two severe thalassemic patients, aged 6 -13 years, were divided into 3 groups according to the frequency of transfusion: 1) high transfusion: more than 12 times/year. 2) low transfusion: 6-12 times/year. 3) occasional transfusion: less than 5 times/year. The appearance and dentition were evaluated and compared among groups. Most subjects in the high transfusion group had a normal appearance and a class I molar and incisor relationship with normal overjet and overbite. More than half of subjects in the low and occasional groups showed craniofacial abnormalities and malocclusion, particular in the occasional group. Frequency of transfusion has an effect on craniofacial appearance and dental occlusion; only high frequent transfusions were effective in preventing craniofacial and dental defects.

INTRODUCTION

Thalassemia is a group of inherited blood disorders characterized by a defect in synthesis of polypeptide chains of globin in red blood cells. The imperfect hemoglobin results in destruction of the red blood cells leading to chronic anemia. The disorders are classified either by the defective globin chains or severity of clinical signs and degree of anemia. The most severe type, homozygous alpha-thalassemia, causes the patient to die inutero or survive only a few hours after birth. Children with homozygous beta - thalassemia or severe beta - thalassemia/hemoglobin E (HbE) survive longer but suffer with anemia. They present with pallor, growth retardation, a high risk for infection, and hepatosplenomagaly. Their clinical manifestations show skeletal abnormalities due to hyperactivity of bone marrow compensating for the anemia. Many studies have reported the typical facial appearance of these patients, described as ro-

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dent face (Baker, 1964; Kaplan *et al*, 1964; Van Dis and Langlais, 1986). They have maxillary enlargement, prominent cheek bones, saddle nose, retraction of the upper lip, protrusion of the anterior teeth, large spaces between teeth, an open bite and varying degrees of malocclusion (Salehi *et al*, 2007).

Hematopoietic stem cell transplantation is a curative form of treatment but is limited to an HLA-identical donor. Therefore, most severe thalassemic patients survive by having blood transfusions, splenectomy when indicated and iron chelation. The transfusions increase the hemoglobin level, reduce hypoxia and suppress erythroid marrow expansion (Cavill *et al*, 1978; Pootrakul *et al*, 1981; Cazzola *et al*, 1995). Many studies have reported the effectiveness of blood transfusions for promoting growth (Kattamis *et al*, 1970; Viprakasit *et al*, 2001), increasing the quality of life (Torcharus *et al*, 1993) and preventing bone deformities (Piomelli *et al*, 1969). Salehi *et al* (2007) noted a reduction in orofacial complications in beta-thalassemia patients during the last decade because of early diagnosis and regular blood transfusions. However, the regimen for optimal blood transfusions that inhibits craniofacial deformity and promotes normal dentition is still unclear.

The purpose of the present study was to evaluate the effect of different transfusion regimens on craniofacial appearance and dentition in severe thalassemic patients.

MATERIALS AND METHODS

The present study was approved by the Committee on Human Rights Related to Human Experimentation, Mahidol University, Bangkok, Thailand. Ninety-two thalassemic subjects and their legal guardians agreed to participate and gave written consent before the research started. All subjects were diagnosed as having either homozygous beta-thalassemia or beta-thalassemia/hemoglobin E by hemoglobin electrophoresis criteria. Severe thlassemia were defined as age of onset before 2 years, pre-transfusion hemoglobin level was less than 7 g/dl or hematocrit level lower than 20% and first transfusion started before 4 years. All medical information was reviewed from hospital charts with permission from the subjects and their physicians. The history of the frequency blood transfusions was also assessed from the medical chart and used to classify the subjects into three groups: 1. high transfusion group; received more than 12 transfusions/year; 2. low transfusion group; received 6 -12 transfusions / year; 3. occasional transfusion group; received less than 5 transfusions/year.

All participants were clinically examined for facial pattern, facial profile, craniofacial deformity and their dentition by an investigator who was blinded to the subject transfusion regimen. Craniofacial deformity was assigned to three grades based on criteria modified from Logothetis *et al* (1971) and Abu Alhaija *et al* (2002).

Grade 0: No craniofacial deformity present, normal appearance. Grade 1: Puffiness of eyelids with slight bulging of the cheeks or mild maxilla and frontal bone over growth. Grade 2: Prominent overgrowth of the maxilla and cheek bones, distinct depression of the bridge of the nose and protrusion of anterior teeth.

The descriptive statistics were used to analyze data and presented in frequency tables with numbers and percentages.

RESULTS

Ninety-two subjects, age between 6.42 and 12.92 years with a mean age 9.44 years, were classified into transfusion regimen group: 27 in the high transfusion group**,** 26 in the low transfusion group and 39 in the occasional transfusion group. There were no

Table 1
Clinical characteristic of transfusion groups.

Clinical characteristics	Transfusion group		
	High	Low	Occasional
Number	27	26	39
Chronological age, Mean (SD)	9.69 (1.82)	9.35(1.65)	10.04 (1.96)
Gender: M:F	18:9	17:9	22:17
Diagnosis: Homozygous β-thal : β-thal/HbE	7:20	5:21	3:36
Pre-transfusion Hb (between transfusions)	8.76 ± 0.9	6.08 ± 0.99	5.19 ± 0.67
Frequency of transfusion (per year)	15.83 ± 1.58	8.65 ± 1.57	3.08 ± 1.0
Splenectomy	5	15	16

Table 2
Craniofacial appearance in relation to transfusion therapy.

	High group *n* (%)	Low group *n* (%)	Occasional group *n* (%)
Facial pattern			
Mesocephalic	21 (77.8)	13 (50.0)	12 (30.8)
Dolicocephalic	6 (22.2)	13 (50.0)	27 (69.2)
Brachycephalic	0	0	0
Facial profile			
Straight	25 (92.6)	14 (53.8)	13 (33.3)
Convex	2 (7.4)	12 (46.2)	26 (66.7)
Concave	0	0	0
Craniofacial deformity			
Grade 0	27 (100)	11 (42.31)	4 (10.26)
Grade 1	0	12 (46.15)	21 (53.84)
Grade 2	0	3 (11.54)	14 (35.9)

statistically significant differences in gender and chronological age among the 3 groups. Patients diagnosed as having severe beta-thalassemia/hemoglobin E were the main subjects in the study. The average number received transfusions per subject per year was significantly different among the groups. The characteristic of the subjects in the groups are shown in Table 1.

The craniofacial and dentition findings among the subjects of the three groups are shown in Tables 2 and 3. More than half the subjects in the occasional transfusion group presented with a long narrow face, convex profile and class II molar and incisor abnormalities with a large overjet. Most of subjects (89%) in this group also had craniofacial deformities. The majority subjects with the most severe craniofacial abnormalities were in this group. In the high transfusion group, a large number of subjects had an ovoid face, well balanced features, normal

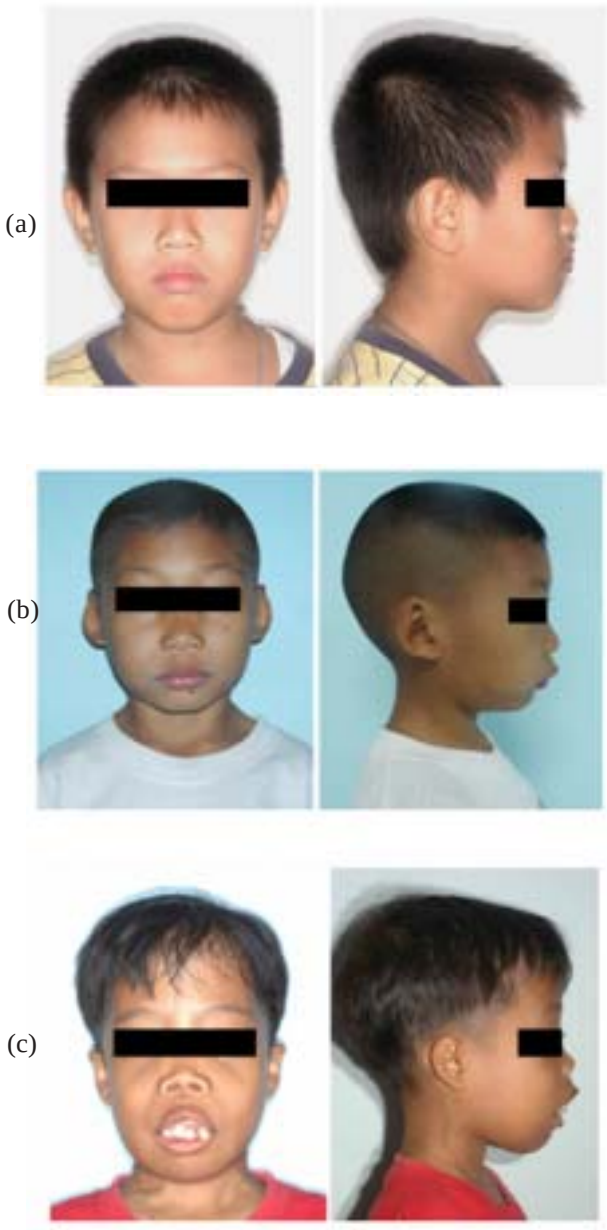

Fig 1–The appearance of severe thalassemic subjects with different transfusion regimens. Subject in Fig 1a was in the high transfusion group and presents with a normal appearance, whereas, the subjects in Fig 1b and 1c received only occasional therapy and have an abnormal appearance and malocclusion.

craniofacial appearance and class I molar and incisor relationship with a normal overjet and overbite. No subjects with severe abnormalities were found in this group.

DISCUSSION

Craniofacial abnormalities and development of malocclusion are common manifestations in severe thalassemic patients. Our findings show the complications were prevented in the high transfusion group. Subjects in this group received early treatment and regular repeated therapy more than 12 times per year with a mean value of about 16 times per year. Many studies have shown that hyperactivity of bone marrow is suppressed as hemoglobin level is increased by transfusion and a high frequency of transfusions increases the hemoglobin level (Baker, 1964; Kaplan *et al*, 1964; Van Dis and Langlais, 1986). Cazzola *et al* (1995) suggested that maintaining a hemoglobin concentration of at least 9 g/dl can suppress erythropoiesis but some centers recommend a level greater than 10 (Propper *et al*, 1980) or greater than 12 g/dl (Piomelli *et al*, 1974). Subjects that received treatment every 3-4 weeks in our study maintained a pretransfusion hemoglobin level of about 8-9 g/dl, which was enough to control abnormal phenotypic expression. This level also resulted in normal growth in a study by Kattamis *et al* (1970). Subjects in the low and occasional groups received transfusions less than 12 times per year with average hemoglobin levels of 6.08 and 5.19 g/dl, respectively, and tended to have gross cosmetic deformity. A previous report found subjects with a hemoglobin level around 7 g/dl had skeletal deformities and subjects with a hemoglobin level around 9 g/dl had limited bone changes (Pippard *et al*, 1982).

The relation between hemoglobin concentration and dental occlusion has been studied. Pusaksrikit *et al* (1987) reported pa-

Table 3
Dentition in relation to transfusion therapy.

	High group	Low group	Occasional group
Incisor relationship, *n* (%)			
Class I	20 (74.1)	12 (46.2)	18 (46.2)
Class II	7 (25.9)	14 (53.8)	21 (53.8)
Class III	0	0	0
Overjet, mm (SD)	2.96 (1.58)	4.04 (2.99)	4.36 (2.67)
Overbite, *n* (%)			
Normal bite	26 (93)	17 (65.4)	24 (61.5)
Deepbite	1 (3.7)	6 (23.1)	9 (23.1)
Openbite	0	3 (11.5)	6 (15.4)
Molar relationship, *n* (%)			
Class I	20 (74.1)	10 (38.5)	13 (33.3)
Class II	7 (25.9)	14 (53.8)	24 (61.5)
Class III	0	0	0
Unclassified	0	2 (7.7)	2 (5.1)

tients with hematocrits less than 24% were predisposed to develop class II teeth abnormalities. This study showed similar results. The most noticeable structural abnormalities were maxillary enlargement producing a convex profile, a large overjet, deepbite and a class II dental relationship. The mandible which consists of dense cortical bone appears normal. However, two previous studies have reported the conflicting findings between clinical appearance and radiographic measurements (Abu Alhaija *et al*, 2002; Amini *et al*, 2007). A cephalometric study showed a normal maxilla length but short mandible (Abu Alhaija *et al*, 2002). This association needs to be further investigated. Several subjects in the low and occasional transfusion groups presented with normal appearance and dentition. This may be because of variation in the relationship between hemoglobin concentration and suppression of erythropoiesis, and genetic reasons for appearance.

High transfusion therapy has been advocated for many years, this study confirms the benefits. However, many patients seek only symptomatic treatment. One of the reasons for this may be the lack of understanding about benefits of therapy and consequences of inconsistent treatment. Therefore, the findings of this study give health care providers the information needed to convince patients to have regular and frequent treatments in order to prevent craniofacial and dental abnormalities in thalassemic patients.

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