HEALTH-RELATED QUALITY OF LIFE IN THAI THALASSEMIC CHILDREN TREATED WITH IRON CHELATION

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Abstract. Thalassemia is a chronic hereditary disease in which patients with severe disease present with anemia during their first year of life. In Thailand, stem cell transplantation is not an option for most patients. Supportive treatments, such as blood transfusions and iron chelation are used. Little data exists regarding the Health Related Quality of Life (HRQoL) of these patients. We conducted a study of the four dimensions of quality of life: physical, emotional, social, and role (school) functioning, using the PedsQL™ 4.0 Generic Core Scale to measure the HRQoL among thalassemic patients at the Hematology Unit, Department of Pediatrics, Phramongkutklao Hospital, during December 1, 2006 - November 30, 2007 to evaluate the quality of life in thalassemic patients treated with three iron-chelating agents. Forty-nine thalassemic patients were enrolled and treated with iron-chelating agents. The mean (SD) age of the patients was 10.61 years (4.33). Fifteen thalassemic patients were treated with desferrioxamine, 18 with deferiprone and 16 with deferasirox. The quality of life (QOL) results show the mean (SD) total summary score was 74.35 (12.42). For the psychosocial health summary, the social and school functioning scores were 85.40 (16.67) and 62.14 (15.84), respectively. The QOL scores of the patients who received desferrioxamine, deferiprone and deferasirox were 75.29 (9.09), 73.91 (15.25) and 73.98 (12.32), respectively ($p = 0.94$). The QOL had no significant differences by age, gender, type of thalassemia or serum ferritin level. Multivariate regression analysis showed no significant differences in clinical severity, age of onset or pre-transfusion hematocrit levels.

Keywords: thalassemic children, health related quality of life, iron chelation

INTRODUCTION

Thalassemia is an inherited blood disorder characterized by a defect in globin chain synthesis in red blood cells. This defect results in red blood cell destruction leading to chronic anemia. Thalassemia is a global public health problem, with an estimated 900,000 babies with this disorder expected to be born during the next 20 years. The incidence of hemoglobin (Hb) E approaches 60% of the population in many regions of Southeast Asia (Vichinsky, 2005). In Thailand, about 30-40% of the population are carriers of alpha- or beta-thalassemia. One percent

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of the Thai population have thalassemia. The combination of thalassemia and any of the various hemoglobinopathy genes results in more than 60 thalassemic syndromes, with varying clinical severity (Panich *et al*, 1992). The disorders can be classified by severity of clinical signs and degree of anemia. Hematopoietic stem cell transplantation is a curative treatment for severe thalassemia, but is limited to human leukocyte antigen (HLA)-identical donors (Resnick *et al,* 2007). Blood transfusions and chelation are necessary in severe patients, especially during childhood, in order to promote growth and prevent bone deformities (Borgna-Pignatti, 2007). Beta-thalassemia major patients successfully treated with transfusion who have good compliance with iron-chelation therapy have long-term survival prospects (Ceci *et al*, 2006; Daar and Pathare, 2006). Patients who receive oral chelation therapy, *ie*, deferasirox, have satisfactory results (Cappellini and Piga, 2008) which results in a positive impact on their daily lives (Cappellini *et al,* 2007). Oral iron chelators such as deferiprone and deferasirox, are now available in Thailand. However, there is little available data regarding the Health Related Quality of Life (HRQoL) in thalassemic children. This study aims to assess the HRQoL of thalassemic children who are receiving blood transfusions and iron chelation.

MATERIALS AND METHODS

A cross-sectional study was conducted among children and adolescents with thalassemia at Phramongkutklao Hospital from December 2006 to November 2007. In this institution, desferrioxamine was the standard iron chelation method. The oral iron chelators deferasirox and deferiprone were introduced for thalassemia patients in May and November 2006, respectively. Patients were approached as they presented for blood transfusions. Written parental informed consent and the child's assent were obtained prior to their participating in the study. The study was approved by the Phramongkutklao Hospital Ethics Committee. Inclusion criteria were thalassemic patients 6-18 years of age who regularly received blood transfusions, had a serum ferritin level >1,000 ng/ml and were being treated with iron chelation.

Sample size calculation

The sample size required for the study was calculated using the formula by Lemeshow *et al* (1990). The sample size should not be <30 times the total number of independent variables. In a previous study (Thavorncharoensap *et al*, 2010) at least one of the two independent variables were correlated with quality of life (pre-transfusion Hb level or age), so the total sample size required was at least 30.

Research instruments

A quality of life assessment was performed using the Pediatric Quality of Life Inventory™ (PedsQL™) 4.0 Generic Core Scale (Thai version). The PedsQL 4.0 includes parallel child self-reports (age ranges 5-7, 8-12 and 13-18 years) and parental proxy reports (age ranges 2-4, 5-7, 8-12 and 13-18 years). Children aged 5-7 years were interviewed by trained interviewers. The parents answered parent poxy questionnaires. This instrument has 23 items, consisting of 8 items on physical functioning, 5 items on emotional functioning, 5 items on social functioning and 5 items on school functioning. Each scale has a score ranging from 0-100, with a higher score indicating higher QOL.

Data analysis

Data were analyzed by Microsoft Excel 2003 and SPSS (Statistical Package for

the Social Sciences) program version 13.0. Clinical characteristics of the patients, total HRQoL score, and summary scores were reported as means and standard deviations (SD). Pearson's correlation, chi-square, ANOVA, and *t*-test were used to examine the relationship between HRQoL and clinical data. Factors influencing the quality of life were later examined by multiple regression analysis. For this study, a patient was classified as having a severe condition if any of the following applied: 1) his/her age at onset of anemia was <2 years, and age at first transfusion was <4 years; 2) a pre-transfusion hematocrit (Hct) level was <20%; or 3) having been diagnosed with homozygous β-thalassemia. With respect to pre-transfusion Hct level, a Hct < 20% was classified as a low blood transfusion regimen and a Hct > 20% as a high transfusion regimen.

RESULTS

The demographic and clinical characteristics of the 49 patients are presented in Table 1. The mean age was 10.6 years; 30 patients (61%) were male; and 39 patients (80%) were in primary or secondary school. Patients were more likely to have β-thalassemia/Hb E (75%). Eighty-one percent of patients received the high transfusion regimen, and the mean (SD) serum ferritin level was 2,473.92 (1,247.38). There were 15 thalassemic patients treated with desferrioxamine, 18 with deferiprone and 16 with deferasirox. Thirty patients (61%) were classified as having a severe type of thalassemia.

The HRQoL scores based on child-self reports compared to proxy reports are presented in Table 2. The mean (SD) for the total summary scores of the child self-reports and proxy reports were 74.35 (12.42) and 68.41 (13.67), respectively ($p = 0.001$). When looking at the two summary scores, the means (SD) for physical functioning and psychological health were 72.32 (17.24) and 75.44 (13.78), respectively. On the subscale for psychosocial health, the study revealed social functioning scored the highest (mean = 85.40; SD = 16.67), followed by emotional functioning (mean = 78.77; SD = 18.35); school functioning, scored the lowest (mean = 62.14; SD = 15.84).

Table 3 shows the HRQoL scores from the child self-report questionaire, classified by patient characteristics. Younger patients were more likely to have higher total summary scores than older patients. When looking at each summary score, gender, age, diagnosis, severity, iron chelation treatment, serum ferritin level, type of payment and education level were not significantly related to each other ($p > 0.05$).

Relationships between HRQoL scores and patient characteristics are presented in Table 4 and calculated with the Pearson's correlation coefficient. Serum ferritin, pretransfusion Hct level, age, diagnosis, type of iron chelation and type of payment were not significant predictors of HRQoL.

Table 5 shows the results of multivariate regression analysis of the examined factors associated with the total summary score. Severity, age and pretransfusion Hct level were not significant predictors of HRQoL (*ie*, total summary score).

DISCUSSION

Assessment of HRQoL among thalassemic patients in this study showed psychosocial health had a higher score than physical health, especially emotional functioning, which differs from the findings of a previous study (Pakbaz *et al*,

Table 1
Patient characteristics.

Clinical characteristics of thalassemia patients	*n* = 49 (SD)
Age (years)[a]	10.61 (4.33)
Gender[b]	
Male	30 (61.2)
Female	19 (38.8)
Age (years)[b]	
2-4	4 (8.2)
5-7	8 (16.3)
8-12	17 (34.7)
13-18	20 (40.8)
Diagnosis[b]	
β-thalassemia/Hb E	37 (75.5)
Homozygous β-thalassemia	7 (14.3)
Hemoglobin H disease	5 (10.2)
Age at onset of anemia (months)[a]	35.45 (29.81)
Age at first transfusion (years)[a]	3.22 (2.38)
Type of blood transfusion[b]	
Low transfusion regimen (Hct < 20%)	9 (18.4)
High transfusion regimen (Hct > 20%)	40 (81.6)
Pre-transfusion Hct level[a]	24.67 (2.59)
Serum ferritin level[a] (ng/ml)	2,473.92 (1,247.38)
Iron chelation treatment[b]	
Desferrioxamine	15 (30.6
Deferiprone	18 (36.7)
Deferasirox	16 (32.7)
Severity[b]	
Yes	30 (61.2)
No	19 (38.8)
Education level[b]	
Kindergarten	5 (10.2)
Primary school	19 (38.8)
Secondary school	20 (40.8)
Higher than secondary school	5 (10.2)
Type of payment[b]	
Out-of-pocket	9 (18.4)
Civil Servant Medical Benefit Scheme	14 (28.6)
Universal Coverage	26 (53.1)

[a]Data given as mean (SD); [b]Values are presented as number (percentage)

2005; Messina *et al*, 2008). The medical therapy of these patients should be supplemented with psychological aid and psychiatric treatment (Messina *et al*, 2008). The recognition and management of the psychological problems that accompany chronic physical illnesses, including thalassemia, will optimize treatment

Table 2
Quality of life scores, child self-report *vs* proxy.

Quality of life domain	Child self-report (n = 49)	Proxy (n = 49)	p-value
	Mean ± SD	Mean ± SD	
Total summary score	74.35 ± 12.42	68.41 ± 13.67	0.001
Physical functioning	72.32 ± 17.24	66.07 ± 18.50	0.004
Psychosocial health	75.44 ± 13.78	69.65 ± 13.25	0.005
Emotional functioning	78.77 ± 18.35	75.30 ± 17.89	0.200
Social functioning	85.40 ± 16.67	76.02 ± 18.02	0.001
School functioning	62.14 ± 15.84	57.65 ± 17.20	0.087

outcomes and HRQoL (Shaligram *et al*, 2007).

Ismail *et al* (2006) used the PedsQL 4.0 Generic Core Scale to assess the HRQoL in thalassemic patients and healthy children. The mean (SD) total summary scores in thalassemic and healthy children were 68.91 (12.12) and 79.76 (11.60), respectively. HRQoL scores obtained from the present study were somewhat higher. This might be due to differences in country-specific characteristics. Another reason that could account for the difference in HRQoL scores between the previous study (Ismail *et al*, 2006) and this study is that most of the patients had thalassemia intermedia. About 75% and 10% were diagnosed with β-thalassemia/Hb E and Hb H disease, respectively, and 80% of them had received a high transfusion regimen.

When looking at subdomains of HRQoL, the school functioning subscale scored the lowest. Frequently missing school for hospital visits, and a lack of energy when performing academic activities, had a significant negative impact on the children's HRQoL.

From a previous study, iron chelation therapy (ICT) with desferrioxamine and deferiprone appeared to negatively impact HRQoL (Payne *et al*, 2008). The HRQoL of oral administration of an iron-chelating agent, such as deferasirox, a once-daily oral treatment, was high when compared with subcutaneous infusion of desferrioxamine (Osborne *et al*, 2007). In the present study, 82% of the patients receiving ICT were covered by the Civil Servant Medical Benefit Scheme or Universal Coverage, while 18% paid out-of-pocket; the HRQoL scores for each of the ICT groups were not different (p = 0.94). Higher scores were found for social and emotional functioning, while school functioning was the lowest.

A limitation of this study, as previously mentioned, is the absence of HRQoL scores for healthy children in Thailand. As a result, the true magnitude of thalassemia's impact on HRQoL is difficult to estimate. Another limitation was the purposive sampling of the setting might limit the extent to which the results could be extrapolated to patients in other settings. Further research of qualitative and quantitative type using validated instruments among patients receiving iron-chelating therapy are needed to further understand

Table 3
Quality of life scores, child self-report classified by patient characteristics.

	Total score	Physical functioning	Psychological functioning	Emotional functioning	Social functioning	School functioning
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years) (n = 49)						
2-4 (n = 4)	80.43 (2.51)	67.19 (21.88)	87.5 (9.95)	97.5 (5)	92.5 (15)	72.5 (12.58)
5-7 (n = 8)	70.79 (15.28)	69.53 (15.47)	71.46 (15.72)	75 (24.49)	82.5 (17.53)	56.88 (14.38)
8-12 (n = 17)	70.2 (11.64)	67.46 (19.07)	71.67 (11.09)	77.06 (12)	80.88 (19.22)	57.06 (13.24)
13-18 (n = 20)	78.1 (12.05)	78.59 (14.49)	77.83 (14.63)	78 (20.55)	89 (14.01)	66.5 (17.55)
p-value	0.147	0.209	0.130	0.198	0.379	0.116
Gender (n = 49)						
Male (n = 30)	74.24 (13.43)	74.06 (17.33)	74.33 (13.6)	80.33 (16.55)	83.83 (17.8)	58.83 (15.74)
Female (n = 19)	74.54 (11)	69.57 (17.21)	77.19 (14.27)	76.32 (21.14)	87.89 (14.84)	67.37 (14.94)
p-value	0.935	0.380	0.485	0.461	0.412	0.066
Diagnosis (n = 49)						
β-thalassemia/Hb E (n = 37)	67.17 (19.99)	56.88 (17.17)	72.67 (24.31)	80 (25.74)	80 (29.37)	58 (22.53)
Homozygous β-thalassemia (n = 7)	76.47 (11.16)	76.52 (15.23)	76.44 (12.86)	80.68 (18.15)	85.54 (15.27)	63.11 (14.74)
Hemoglobin H (n = 5)	68.32 (10.4)	61.16 (18.39)	72.14 (10.44)	67.86 (10.75)	88.57 (14.64)	60 (18.48)
p-value	0.110	0.008	0.680	0.239	0.686	0.746
Severity * (n = 49)						
Yes (n = 30)	75.87 (12.87)	75.52 (16.37)	76.06 (14.61)	81 (18.77)	86 (16.53)	61.17 (16.54)
No (n = 19)	71.97 (11.6)	67.27 (17.81)	74.47 (12.71)	75.26 (17.6)	84.47 (17.31)	63.68 (14.99)
p-value	0.289	0.103	0.700	0.291	0.758	0.593
Iron-chelation treatment (n = 49)						
Desferrioxamine (n = 15)	75.29 (9.09)	71.04 (15.95)	77.56 (12.44)	83.67 (13.69)	87.67 (12.94)	61.33 (18.46)
Deferiprone (n = 18)	73.91 (15.25)	70.66 (20.11)	75.65 (15.69)	77.5 (18.41)	83.89 (19.6)	65.56 (16.53)
Deferasirox (n = 16)	73.98 (12.32)	75.39 (15.52)	73.23 (13.24)	75.63 (21.98)	85 (17.03)	59.06 (12.28)
p-value	0.943	0.694	0.690	0.453	0.811	0.487
Serum ferritin level						
< 2,500 ng/ml (n = 29)	73.01 (13.74)	70.69 (17.1)	74.25 (14.72)	78.79 (18.5)	84.14 (18.37)	59.83 (14.73)
>2,500 ng/ml (n = 20)	76.3 (10.24)	74.69 (17.62)	77.17 (12.49)	78.75 (18.63)	87.25 (14.09)	65.5 (17.16)
p-value	0.368	0.431	0.473	0.994	0.526	0.222

Type of payment						
Out-of-pocket (n = 9)	77.29 (14.6)	72.57 (19.06)	79.81 (16.55)	86.67 (15.21)	86.67 (21.65)	66.11 (16.73)
Civil Servant Medical Benefit Scheme (n = 14)	75.47 (14.87)	72.32 (21.58)	77.14 (14.67)	78.93 (20.96)	89.29 (14.53)	63.21 (16.48)
Universal Coverage (n = 26)	72.74 (10.32)	72.24 (14.59)	73.01 (12.28)	75.96 (17.72)	82.88 (16.07)	60.19 (15.52)
p-value	0.600	0.999	0.390	0.327	0.505	0.609
Education level						
Kindergarten (n = 5)	80 (2.38)	68.75 (19.26)	86 (9.25)	96 (5.48)	94 (13.42)	68 (14.83)
Primary school (n = 19)	72.14 (13.63)	70.39 (19.39)	73.07 (13.43)	76.32 (17.31)	83.42 (18.64)	59.47 (12.9)
Secondary school (n = 20)	74.08 (10.81)	74.69 (14.01)	73.75 (13.07)	75.5 (18.27)	84.5 (16.13)	61.25 (17.98)
Higher than secondary school (n = 5)	78.26 (19.31)	73.75 (22.6)	80.67 (18.95)	84 (24.34)	88 (15.25)	70 (18.71)
p-value	0.557	0.844	0.213	0.120	0.633	0.485

Table 4
Relationship between HRQoL score and patients' characteristics by Pearson's correlation coefficient.

	Pearson's correlation coefficient					
	Total summary score	Physical functioning	Psychological functioning	Emotional functioning	Social functioning	School functioning
Serum ferritin level (ng/ml)	0.091	0.126	0.041	-0.061	-0.009	0.189
Pre-transfusion Hct level (%)	0.154	0.159	0.106	0.097	-0.031	0.197
Age (years)	0.083	0.204	-0.021	-0.141	0.056	0.049
Diagnosis	-0.021	-0.002	-0.028	-0.188	0.123	0.015
Type of iron chelator	-0.042	0.103	-0.126	-0.175	-0.063	-0.061

Table 5
Multivariate regression analysis result.

	β	SE (β)	*p*-value
Constant	57.295	17.780	0.002
Severity[a]	-3.566	3.685	0.338
Age (years)	0.177	0.419	0.675
Pretransfusion Hct level (%)	0.671	0.700	0.343

$R^2 = 0.048$; Y = Ln (total summary score)
[a]Age at onset <24 months and age at first transfusion <4 years

issues and improve patient HRQoL (Abetz *et al*, 2006).

In conclusion, the quality of life of thalassemic children showed improvement in psychosocial health, and social functioning with treatment. The three iron-chelating agents showed no differences in impact on the HRQoL.

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