Quality of life in transfusion-dependent thalassaemia patients on desferrioxamine treatment

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ABSTRACT

Introduction: The quality of life of transfusion-dependent thalassaemia patients is affected by the disease itself and iron overload complications from repeated blood transfusion. Desferrioxamine has been used to remove the excess iron, resulting in decreased mortality and morbidity. In Malaysia, a significant proportion of the transfusion-dependent thalassaemia patients are not prescribed desferrioxamine, due to its high cost, especially as it is not subsidised by the government. The aim of this study was to measure the quality of life of thalassaemia patients on desferrioxamine treatment.

Methods: A cross-sectional study was performed on all transfusion-dependent thalassaemia patients on follow-up at two tertiary hospitals in Kuala Lumpur, Malaysia, in 2005. Quality-of-life scores were measured by using the translated MOS SF-36 questionnaires, while diseases related to iron overload complications were obtained from the medical records. Use of desferrioxamine was elicited through interviews and validated by drug records. Quality-adjusted life-years (QALYs) presented were formulated from residual life-years and quality-of-life scores.

Results: A total of 112 transfusion-dependent thalassaemia patients were recruited, with 54 (48 percent) and 58 (52 percent) patients on sub-optimum and optimum desferrioxamine treatments, respectively. QALYs were higher in patients on optimum desferrioxamine (9.04, standard deviation [SD] 2.46) than patients on sub-optimum desferrioxamine (5.12, SD 2.51). QALYs were associated with the level of serum ferritin, iron overload complications and total family income.

Conclusion: Optimum desferrioxamine usage reduces iron overload complications and provides a better quality of life.

Keywords: desferrioxamine treatment, iron overload complications, quality of life, quality-adjusted life-years, transfusion-dependent thalassaemia

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INTRODUCTION

Thalassaemia is a genetic disorder affecting globin chain synthesis with various clinical manifestations, depending on the number and the type of globin chain affected. The more severe forms are beta-thalassaemia major, which warrants regular blood transfusion at an early age, and thalassaemia intermedia which presents later and require less frequent transfusions. The aim of regular blood transfusions is to eliminate the primary complication of severe thalassaemia by ameliorating anaemia and suppressing erythropoiesis. Given that patients are usually transfused at an early age, many develop complications of iron overload and blood transmitted infections. Among the common diseases that are related to high iron load are heart failure, liver fibrosis, diabetes mellitus, growth retardation and delayed puberty.[1] Iron chelator is needed to remove the toxic iron and desferrioxamine (desferrioxamine B methanesulphonate, or clinically known as Desferal [Norvatis]) had been proved to reduce the iron load and the complications of iron overload.[2] Since the introduction of desferrioxamine, the morbidity and mortality related to thalassaemia have been reduced significantly.

The quality of life (QOL) should be considered an important index of effective treatment. An assessment of QOL differs from other forms of medical assessment in that it focuses on the individuals' own views of their well-being and assesses other aspects of life, giving a more holistic view of well-being. Several studies had looked into the domains of quality life that is affected by thalassaemia and its treatment. Pakbaz et al suggested that emotional functioning is one of the impaired QOL domain in thalassaemia patients;[3] however, several other QOL studies in adult thalassaemia had shown that the treatment and cultural differences did not have any major effect on

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Table I. Quality-of-life scores of transfusion-dependent thalassaemia patients on sub-optimum and optimum desferrioxamine dosage.

Health domains	Sub-optimum dosage* (n = 54)	Optimum dosage* (n = 58)	p-value
Physical function	69.33 ± 27.52	76.43 ± 20.80	0.018
Physical role	55.29 ± 38.46	54.02 ± 38.07	0.745
Body pain	15.15 ± 19.97	12.71 ± 15.98	0.165
General health	49.56 ± 13.29	50.88 ± 11.55	0.546
Vitality	47.50 ± 8.72	47.12 ± 9.14	0.982
Social function	47.36 ± 16.76	48.66 ± 11.63	0.152
Emotional role	66.03 ± 42.00	67.56 ± 35.45	0.072
Mental health	57.08 ± 7.52	56.14 ± 8.96	0.424
Mental composite scores	41.95 ± 7.03	41.95 ± 5.49	0.196
Physical composite scores	35.73 ± 8.68	36.78 ± 7.5	0.058

* expressed as mean and standard deviation

their QOL. A case-control study which measured the QOL in thalassaemia children was conducted in Hospital Kuala Lumpur by Ismail et al, where PedsQL 4.0 was used as the health-related QOL instrument. The questionnaires were administered to thalassaemia children receiving blood transfusions and to healthy school children of the same age range as the control group. The authors reported that the scores for physical, social and school functioning domains in thalassaemia patients were significantly lower than the healthy controls. However, they did not differentiate the scores according to usage of desferrioxamine and the presence of iron overload complications.[4] A study by Delea et al measured the QOL of thalassaemia patients on desferrioxamine treatment and those on deferasirox, an oral iron chelator. They reported that deferasirox resulted in a gain of 4.4 quality-adjusted life-years (QALYs) in patients not on desferrioxamine and 2.7 QALYs in patients already on desferrioxamine.[5]

In Malaysia, it is estimated that only about 40%–50% of the transfusion-dependent thalassaemia patients in the government hospitals are using desferrioxamine at the correct dose, and many of these patients had a high iron load in their body.[6] Reasons for not complying to the guidelines are not only due to the inconvenience of injecting desferrioxamine, but also because of the exorbitant cost of this treatment for a long duration. At the general hospitals, the Ministry of Health Malaysia subsidises all treatment in relation to thalassaemia except the provision of desferrioxamine, which patients have to obtain at their own expenses or find sponsorships. The aim of this study was to show that treatment of transfusion-dependent thalassaemia patients with desferrioxamine would provide better QOL for patients despite having to bear the cost and inconveniences of desferrioxamine injections. The specific objectives of this study were: (1) to determine the QOL scores of transfusion-dependent thalassaemia patients according to the status of desferrioxamine usage; (2) to describe the sociodemographic and disease characteristics of patients based on the status of desferrioxamine usage; (3) to measure QALYs and compare groups of patients according to status of desferrioxamine usage; and (4) to identify factors other than desferrioxamine that is associated with QALYs.

METHODS

A cross-sectional study was performed on transfusion-dependent thalassaemia patients on follow-up at the Department of Paediatrics, Hospital Universiti Kebangsaan Malaysia and at the Institute of Paediatrics, Hospital Kuala Lumpur, Malaysia, in 2005. All transfusion-dependent thalassaemia patients with complete medical records during the period 2000–2005 were recruited into the study. The inclusion criteria were patients who were aged six years and above, did not have bone marrow transplant and gave consent. Patients or parents were interviewed on desferrioxamine usage and grouped according to their desferrioxamine status. QALYs were chosen as the outcome indicator in comparing the groups. The QOL scores were obtained through the self-administered medical outcomes study short form 36-item (MOS SF-36) questionnaire, which was translated to Bahasa Malaysia and validated.[7] Patients who were unable to answer the questionnaire themselves were assisted by their parents or guardians. The medical records of the patients were reviewed to determine the serum ferritin levels and to look for the presence of iron overload complications. Data collection was carried out from February 2005 to August 2005. The calculation of QALYs was based on the formulation of quality-adjusted life expectancy (QALE), where the residual life-years were multiplied with the physical composite scores. Chi-square tests, *t*-tests and correlation were performed by using the Statistical

Table II. Sociodemographical profile and disease characteristics of thalassaemia patients according to their desferrioxamine status.

Characteristics	No. (%) patients with sub-optimum dosage (n = 54)	No. (%) patients with optimum dosage (n = 58)	p-value*
Age group (years)			0.051
6–10	8 (15)	10 (17)	
11–15	16 (30)	25 (43)	
16–20	18 (33)	14 (24)	
> 20	12 (22)	9 (16)	
Gender			0.285
Female	29 (53)	27 (47)	
Male	25 (47)	31 (53)	
Ethnicity			0.084
Malay	31 (57)	40 (69)	
Others	23 (43)	18 (31)	
Diagnosis			0.318
Beta-thalassaemia major	46 (85)	43 (74)	
Other thalassaemia	8 (15)	15 (26)	
Spleen status			0.058
No splenectomy	34 (63)	38 (66)	
Splenectomy	20 (37)	20 (34)	
Mean Hb (mmol/L)	8.53	8.46	0.638
Mean blood volume transfused (L/year)	6.92	7.21	0.631
Mean and SD serum ferritin (µg/L)	7,863.29 ± 4,089.29	5,843.93 ± 3,068.35	0.004
Mean and SD age started on desferrioxamine (years)	10.6 ± 5.66	8.3 ± 4.38	0.033
Educational level of parents			0.052
Up to primary level	11 (20)	6 (10)	
Up to secondary level	37 (69)	36 (62)	
Above secondary level	6 (11)	16 (28)	
Total monthly family income (RM)			0.016
≤ 2,000.00	39 (72)	32 (55)	
> 2,000.00	15 (28)	26 (45)	
Patient with iron overload complication/s	28 (60)	19 (40)	0.008

*Chi-square test was performed to show the differences between the groups. p-value is statistically significant at < 0.05.

Package for Social Science version 11.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was set at a p-value < 0.05. Results are presented as proportions, means and standard deviation. This study was approved by the ethics committees of the Ministry of Health Malaysia and from both hospitals. Written consent was also obtained from the patient's parents or guardians.

For this study, the terms used are defined as follows: transfusion-dependent thalassaemia patients refer to thalassaemia patients on blood transfusions at intervals of at least eight weeks, and had been on blood transfusion for at least five years. Optimum group refers to thalassaemia patients on desferrioxamine for the last two years at doses < 40 mg/kg/day, for five days a week; while sub-optimum group comprises thalassaemia patients on desferrioxamine for the last two years at doses < 40 mg/kg/day and less than five days a week. Iron overload complication refers to diseases related to iron overload, such as cardiac disease, abnormal liver functions, diabetes mellitus and impaired oral glucose tolerance test (OGTT). Cardiac disease describes clinically-manifested symptoms of heart failure, with or without abnormal systolic ejection detected through echocardiogram, and with or without arrythmias on electrocardiogram. An abnormal liver function test is when the serum alanine transaminase > 100 mmol/L. Diabetes mellitus is defined as a fasting blood glucose level ≥ 126 mg/dL (7 mmol/L) or a two-hour post-glucose load ≥ 200 mg/dL (11.11 mmol/L). Impaired OGTT is diagnosed when the fasting glucose is < 6 mg/dL and the two-hour post-glucose load is within the range of 140–200 mg/dL.[8]

RESULTS

The total number of transfusion-dependent thalassaemia patients at both hospitals was 115. However, three patients who did not give consent and were excluded from the study, were the patients who had never been on any iron chelator. 48% (54 patients) were receiving desferrioxamine injections at a sub-optimum dose, while 52% (58 patients) were on an optimum desferrioxamine

Table III. QALYs in transfusion-dependent thalassaemia patients based on various factors.

Variables	QALYs (physical composite score)	QALYs (mental composite score)	p-value*
Age group (years)			< 0.05
6–10	9.93 (2.51)	10.89 (2.21)	
11–15	8.35 (2.40)	9.82 (2.60)	
16–20	6.24 (2.65)	6.69 (2.32)	
> 20	3.81 (2.17)	4.60 (2.33)	
Diagnosis			> 0.05
Beta-thalassaemia major	7.00 (3.23)	7.92 (3.39)	
Beta-thalassaemia intermedia	8.09 (2.75)	9.10 (2.89)	
HbE thalassaemia	4.01 (0.51)	7.80 (2.85)	
Gender			> 0.05
Female	7.04 (3.09)	8.05 (2.92)	
Male	7.26 (3.26)	9.00 (3.67)	
Ethnicity			> 0.05
Chinese	7.45 (2.80)	8.29 (3.01)	
Malay	6.18 (3.49)	7.48 (3.76)	
Indian	8.40 (0)	9.69 (0)	
Others	11.19 (2.07)	11.15 (1.25)	
Desferrioxamine status			< 0.05
Sub-optimum	5.12 (2.51)	5.48 (2.48)	
Optimum	9.04 (2.46)	10.24 (2.45)	
Educational level of parents			< 0.05
Primary	5.05 (3.61)	6.21 (3.32)	
Secondary	7.35 (3.07)	8.17 (3.20)	
Tertiary	8.12 (2.44)	9.44 (3.07)	
Total monthly family income (RM)			> 0.05
< 1,000	6.84 (3.50)	7.94 (3.08)	
1,001–2,000	6.67 (3.00)	7.73 (3.45)	
2,001–3,000	7.40 (3.92)	7.90 (3.77)	
> 3,000	8.20 (2.49)	9.19 (2.81)	

* Chi-square test was performed to show the differences between the groups. p-value is statistically significant at < 0.05.

dose. Table I shows the QOL scores which consists of eight dimensions, together with the mental composite scores (MCS) and physical composite scores (PCS). The scores on physical function, general health, social function, emotional role and PCS were slightly higher in the optimum group, compared to the sub-optimum group, while the physical role, body pain, vitality, mental health and MCS were slightly higher in the sub-optimum group than the optimum group. Most of the differences that were observed were not significant except for the score on physical function, which was significantly higher ($p = 0.018$) in the optimum group.

The various characteristics of transfusion-dependent thalassaemia patients with regard to their sociodemographical profile and disease characteristics on sub-optimum and optimum desferrioxamine treatments at both hospitals are summarised in Table II. The mean serum ferritin level, age when desferrioxamine treatment was commenced and the rate of iron overload complications were significantly lower in the optimum group than the sub-optimum group, while the total family income was significantly higher in the optimum than sub-optimum group. QALYs increased with an increased dose of desferrioxamine used (a correlation of 0.232, $p = 0.014$). Based on the status of desferrioxamine usage, QALYs (of the PCS) were higher in thalassaemia patients on optimum compared to sub-optimum desferrioxamine dosage (QALYs 9.04, SD 2.46 and QALYs 5.12, SD 2.50, respectively; $p = 0.000$).

According to the socioeconomic backgrounds, QALYs were significantly different in the various age groups (QALYs lowered as age increased) and at different educational background of the patient's parents (a higher educational background had higher QALYs). However, there was no significant difference in the QALYs according to gender, disease type, ethnic groups and total family income. Table III shows the distribution of QALYs (PCS and MCS), according to the various factors. QALYs were also associated with the serum ferritin level. Fig. 1 shows the correlation between QALYs and serum ferritin levels. There was an inverse relationship between the QALYs (PCS) and serum ferritin levels (a correlation of -0.265, $p = 0.000$). There was significantly higher QALYs in patients without iron overload complications compared to those with iron overload complications, 8.11 ± 3.07 and 5.96 ± 2.88, respectively.

DISCUSSION

The scores for QOL based on the MOS SF-36 questionnaires showed no significant differences in

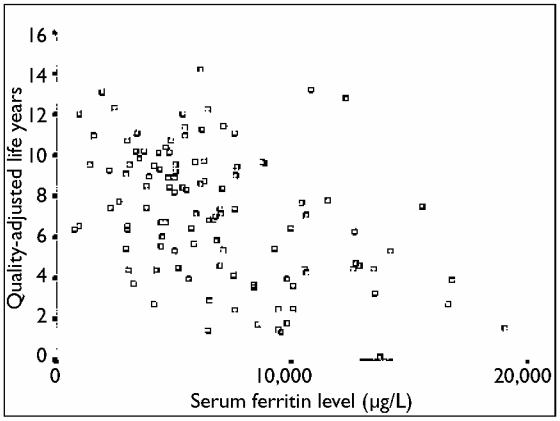

Fig. 1 Scatterplot shows the quality-adjusted life years according to the serum ferritin levels in the transfusion-dependent thalassaemia patients in 2004.

all eight dimensions and the MCS and PCS, except for the physical function dimension. The general well-being of thalassaemia patients, whether they received desferrioxamine at sub-optimum or optimum dose, was not very much affected. Studies had shown that the QOL for non-chelated and fully-chelated thalassaemia patients differed, where the fully-chelated patients had a QOL almost similar to that of normal children, except with regard to body pain.[9]

In general, the reasons that the physical function score for both groups was higher than the other domains were because these patients had been having the disease since childhood, they were not working for a living and as such had not much expectation with regard to physical performance. Those on optimum desferrioxamine dose had a higher physical function score than those on sub-optimum dose, and this could be very much due to the fact that patients on an optimum desferrioxamine dose had less iron overload complications in terms of number of diseases and severity of each disease. Age factor could not be used to explain the difference in the physical function score since the age group distribution is almost similar for both groups. The lowest score was observed for body pain which indicated a low level of freedom from pain in both groups. Every injection of desferrioxamine caused pain and patients were not immune to the pain no matter how frequent and how much they were injected with desferrioxamine.

QALYs based on MCS were higher than QALYs based on PCS. This could be due to the timing of data collection which took place when the patients were having their blood transfusion at the daycare. During the week prior to the blood transfusion, thalassaemia patients were generally weak from anaemic conditions and had faced some limitations in physical activities, while their mental composite remained more or less constant from day to day.

Factors that were associated with QALYs in this study include age of the patient, educational level of the patient's parents, serum ferritin level and rate of iron overload complications. The reason that the QALYs decreases as the age of the patient increases could possibly be due to the patients being able to value health more and realise the limitations of their roles due to the disease as their age advances. The parent's education could have contributed to the understanding of the disease and possibly played a role in helping patients to cope with their disease.

QALYs were also observed to be significantly correlated with serum ferritin levels in the transfusion-dependent thalassaemia patients. The higher the level of serum ferritin, the lower the QALYs observed in these patients. On the other hand, the serum ferritin level is also dependent on the amount of iron (total blood transfused) and the dose of desferrioxamine used. Although the mean total blood volume transfused in both the optimum and sub-optimum groups was of no significant difference, and the mean total dose of desferrioxamine was significantly higher in the optimum than the sub-optimum group, we could not show any correlation between the serum ferritin level and dose of desferrioxamine used.

QALYs were observed to be higher as the dose of desferrioxamine used increases. When grouped according to the status of desferrioxamine usage, thalassaemia patients on optimum desferrioxamine dose were found to have better QALYs than thalassaemia patients on sub-optimum desferrioxamine dose. This could be explained by the lower proportion of patients with iron overload complications in the optimum group compared to the sub-optimum group. Although there was no study that compares the QOL between patients on sub-optimum and optimum desferrioxamine injections, generally the QOL in fully-chelated thalassaemia patients was better than those not on chelation. The study by Delea et al indicated that QALYs were already high in thalassaemia patients on desferrioxamine compared to those not on desferrioxamine, and the addition of oral iron chelator to those on desferrioxamine would increase QALYs further.[5] In this study, the incremental gain of QALYs from switching sub-optimum desferrioxamine to optimum desferrioxamine dosage is 3.92 QALYs.

The educational level of the patient's parents was one of the factors that could determine their level of understanding on the importance of using desferrioxamine at optimum dose and starting treatment at an earlier age. In this study, we observed that the starting age of using desferrioxamine was younger in patients on an optimum desferrioxamine dose compared to those on a sub-optimum dose. However, the proportion of patients

whose parents had an educational level of secondary level and above was of no significant difference in the group of patients using optimum desferrioxamine compared to the group of patients using sub-optimum desferrioxamine. Obviously, those with a higher income would be more able to afford the desferrioxamine treatment at optimum dose. In this study, there were significantly higher proportions of patients with a total family income of more than RM 2,000 in the optimum group compared to the sub-optimum group. By having a higher income, thalassaemia patients not only would use desferrioxamine at the optimum dose, but they would also initiate desferrioxamine injections earlier, as observed in this study. We also know that a higher income is generally associated with higher living standards, and hence, better QOL. Therefore, in this study, the higher QALYs obtained by patients on optimum desferrioxamine should not entirely be attributed to optimum desferrioxamine usage alone.

The accuracy of the study results was very much dependent on the completeness of the patients' medical records. Some data, especially on the serum ferritin level, was not available or not performed on the patients as frequently as other tests. Some routine investigations that were supposed to be done at scheduled intervals to detect sub-clinical cases of iron overload complications were also not performed. Therefore, we could have missed the asymptomatic cases of iron overload complications. A comparison of groups of patients at different desferrioxamine doses with patients never on desferrioxamine before would better demonstrate the effects of desferrioxamine.

In this study, we showed that transfusion-dependent thalassaemia patients on an optimum desferrioxamine dosage had higher QOL scores and higher QALYs than those on a sub-optimum desferrioxamine dosage. Optimum desferrioxamine dosage could lower the levels of serum ferritin, which was associated with a lower rate of iron overload complications. Although higher income has been associated with a better QOL due to higher living standards, in this study, it also enabled patients to start desferrioxamine treatment early and at optimum dose.

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