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Original Research

Effect of drug use calendar on adherence to iron chelation therapy in young thalassemia patients

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Abstract

Background: Regular blood transfusions in thalassemia patients can lead to severe complications and iron chelation therapy is required as a treatment. Thalassemia is common in Thailand and the drugs used in iron chelation therapy are deferoxamine and deferiprone. Adherence to the therapy is a key factor for treatment success. **Objective:** To assess the impact of a drug use calendar on deferiprone and deferoxamine adherence in young thalassemia patients. **Methods:** A total of 86 young thalassemia outpatients at a Thai tertiary care hospital were recruited into the study. Patients were stratified into two groups based on self-assessment of adherence using a visual analogue scale. One group (n=41) was given a calendar with the schedule of drug use in addition to counselling as standard pharmaceutical care. The second group (n=45) only received the counselling. Adherence to iron chelation therapy was assessed by deferiprone pill or deferoxamine vial counts on six visits (V1 to V6) and results were compared between visits and groups using a multilevel linear regression model. Change in serum ferritin levels after 6 visits (n = 81) were compared using a linear regression model. Results: Adherence significantly increased in both the calendar and non-calendar groups for deferiprone mono- and combination-therapy and for deferoxamine monotherapy. In the calendar groups, average adherence increased by between 2.05 and 5.66% per visit compared to increases of 0.31 to3.92% per visit in the non-calendar groups. A significant difference in the increase in adherence per visit between the calendar and non-calendar groups was only observed for deferiprone monotherapy (3.03% SEM = 0.49vs 1.42% SEM =0.49, respectively, P-value = 0.0078). The serum ferritin level decreased in the calendar group by 20.25ng/mL (SEM = 23.80) and increased in the non-calendar group by 59.63 ng/mL (SEM = 23.01, P-value = 0.0147). Conclusion: Provision of a drug use calendar improved adherence to deferoxamine and deferiprone and decreased serum ferritin levels in young Thai thalassemia patients over the improvements obtained from standard counselling.

Keywords: Iron; Chelation therapy; Adherence; Thailand; Thalassemia

INTRODUCTION

Thalassemia is a group of blood disorders characterised by reduced synthesis of the α- or β-globin chains in haemoglobin.[1] Thalassemia can be divided into transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT), depending on the clinical severity.[1] In Thailand, TDT is used for patients with homogenous β^0-thalassemia, haemoglobin E/β-thalassemia and non-deletional α-haemoglobin H disease also known as HbH Constant Spring.[2] These patients show severe clinical manifestations and require regular blood transfusions for survival, whereas NTDT patients exhibit milder symptoms and require more infrequent blood transfusions for the correction and prevention of manifestations such as growth retardation, extramedullary erythropoiesis and bone changes. NTDT is more common in paediatric patients. Treatment options for this disease include stem cell transplantation, or gene therapy and pharmaceutical agents that improve erythropoiesis.[3] Stem cell transplantation is the only curative therapy for thalassemia but it cannot be provided to all patients due to limited availability of donors, high costs, and the chance of treatment-related mortality and it is mainly used for β thalassemia.[4] Gene therapy and the use of agents to improve erythropoiesis such as Janus kinase 2 (JAK2) inhibitors and activin receptor-II ligand traps are promising treatments, but the data regarding their use is still limited.[3] Therefore, the current standard treatment for thalassemia is regular blood transfusions, which suppress abnormal erythropoiesis and help patients to maintain normal physical activity.[3,5] However, the regular administration of blood can result in iron overload, which can lead to long-term complications such as cardiovascular disorders, hepatic disorders, malignancies, cerebrovascular disorders and endocrine abnormalities.[6] Iron chelation therapy is used to maintain an optimal level of ferritin, the main storage form of iron and is administered when serum ferritin levels are more than 1000 ng/mL in TDT patients or 800 ng/mL in NTDT patients, respectively.

Three iron chelators are used for the treatment of iron overload.The standard choice is subcutaneous

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deferoxamine, which requires infusion over 8–12 hours, 5–7 days per week.[4] The other chelators, deferiprone and deferasirox, are available in oral form. Deferiprone is normally taken three times per day and deferasirox is taken once daily.[4] Iron chelation therapy requires careful monitoring and good adherence to the dosage regimen to achieve good therapeutic outcomes.[7] Previous studies have revealed adherence rates to deferoxamine, deferiprone and deferasirox in paediatric patients of 59-83.3%, 79-98%, and 90-95%, respectively.[8-12] These studies employed several different methods to assess adherence including patient interviews to ask about adherence, pill or vial counts, self-assessment by patients, and serum ferritin level. It has been suggested that education and counseling interventions that include pill box count, diaries, and pharmacist-provided services improve iron chelation therapy adherence,[9,13] and in one study, using multiple interventions in combination appeared to result in a higher adherence rate.[14]

In Thailand, about 12,000 cases of thalassemia are diagnosed each year.[5] One survey estimated the prevalence of TDT in Thailand to be 29.33% and reported that all TDT patients had disease-related complications including gallstones, extramedullary haematopoiesis and pulmonary hypertension.[15] Blood transfusion with iron chelation therapy is the mainstay treatment in Thailand because of limited access to stem cell transplant therapy in this region. Due to the high cost of once-daily oral deferasirox, the standard or universal medical care scheme in Thailand only covers subcutaneous deferoxamine and oral deferiprone. A previous study showed that adherence to iron chelation therapy was poor in Thai patients,[11] but no previous study in Thailand has implemented an intervention to try and improve adherence to iron chelation therapy. Therefore, this study explored adherence to deferoxamine and deferiprone in young Thai thalassemia patients before and after implementation of a drug use calendar intervention designed to improve adherence rates.

METHOD

Study procedure

This study was a longitudinal controlled study.The protocol was approved by the Institutional Review Board before commencing the study.The study was conducted in accordance with the Declaration of Helsinki and the ICH Good Clinical Practice guidelines determined by The Khon Kaen University Ethics Committee for Human Research.Informed, written consent was obtained from the patients and/or their guardians prior to their inclusion in the study.

Participants

Patients aged 2-18 years who attended the Paediatric Thalassemia Outpatient Unit at Srinagarind Hospital, Khon Kaen University, Thailand and received blood transfusions with deferoxamine and/or deferiprone to prevent iron overload were invited to participate in this study. All patients were given leukocyte-depleted antigen-matched packed red blood cells at10-15mL/kg every 3-4 weeks to maintain their pre-transfusion haemoglobin level above 9 g/dL. Ninety-two patients were originally approved as eligible for the study unit but six patients were excluded due to discontinuation of iron chelation therapy during the study period.

Iron chelation therapy

There were three treatment patterns of iron chelation therapy in this study. These were deferiprone monotherapy, deferoxamine monotherapy and combination therapy of deferiprone and deferoxamine. The initial dose of oral deferiprone for the patients was 30-50 mg/kg/day divided into two or three doses.In the absence of side effects, the deferiprone dose was increased to 75-100 mg/kg/day. Deferoxamine was infused at 20-30 mg/kg/day for 5-7 days/week in monotherapy or 2-5 days/week in combination with deferiprone. The drugs doses were adjusted according to the serum ferritin levels, which were assessed every 3-6months.The target serum ferritin value was below 300 ng/mL.

Intervention procedures

The patients were randomly stratified into two groups for each treatment type (deferiprone, deferoxamine, and combination of deferiprone and deferoxamine). Patients in the first group were given a calendar to remind them of the schedule of drug use plus counselling by the pharmacist as standard pharmaceutical care (calendar group). Patients in the second group only received counseling by the pharmacist (non-calendar group). The calendar contained tables with dates and times and the participants were expected to cross off the dates and times when they used the medications. To complete the study, the participants had to present at the hospital for 6 visits, 3-6 weeks apart from each other, as routinely defined by the hospital.

Counselling was defined as a brief session with the pharmacist to provide patients and their guardians with information about the disease state and the treatment plan for individual patients. The importance of a regular drug use schedule and lifestyle management were emphasized as part of the counselling. Lifestyle management information included advice to avoid high iron containing foods and dietary or herbal supplements as well as management of adverse drug events.Patients who missed at least one dose of the chelating agent between visits were asked to give the reason. Advice regarding how to improve adherence was given as a standard pharmaceutical care.

Outcomes

Clinical and laboratory data were recorded for each patient before commencing the study and on each visit as a part of routine monitoring. These included the

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diagnosis of concurrent diseases, history of thalassemia treatment, duration of iron chelation therapy, and serum ferritin level on visits one and six (V1 and V6). On each visit, data regarding the dosage regimen and the remaining amount of iron chelating agents were recorded. The outcomes of this study were adherence to the drug treatment and changes in serum ferritin levels from V1 to V6. Baseline adherence was assessed by the patients or their guardians using a Visual Analog Scaleat the beginning of the study (before V1). It was graded into 3 levels which included excellent (adherence greater than 90%), good (adherence 50-90%) and poor (adherence below 50%). This classification was used for stratification of the patients into calendar and non-calendar groups. Adherence for the study period (V1-V6) was assessed by counting the amount of medication (pill count for remaining deferiprone and used vial count for deferoxamine) on each hospital visit. Adherence rate was calculated by the following equations and the changes of serum ferritin were calculated using the data on V1 and V6.

Adherence to deferiprone = [(Number of pills last visit-Number of pills brought to clinic) ×100]/ (Prescribed pills per day ×days since last visit)

Adherence to deferoxamine = [(Number of used vials brought to clinic) ×100]/ (Number of prescribed vials each visit)

Data analysis

The data were analysed by STATA 16 (College station, TX: StataCorp LP). Demographic characteristics are presented by descriptive analysis. Continuous variables are described as means with standard deviations or medians with interquartile range, as appropriate. Categorical variables are described as frequencies and percentages. Normal distribution of the drug adherence and serum ferritin level datawere tested by the Shapiro-Wilk test. A multilevel linear regression model was used to quantify and compare the average change of adherence per visit for both groups. Differences in serum ferritin levels between V1 and V6 were compared between the calendar and non-calendar groups using a linear regression model. Baseline adherence and baseline serum ferritin levels were adjusted in the models. All p-values were 2-tailed, and $p<0.05$ was considered statistically significant.

Table 1. Demographics and medical background of young thalassemia patients at baseline

Characteristic		Calendar group (n = 41)	Non-calendar group (n = 45)
Mean age (year)		12.29 (SD = 3.65, range 6-17)	12.04 (SD = 3.98, range 5-17)
Adolescent		23	22
Type of thalassemia	β-thal/HbE	23	25
	HbH with CS	9	11
	EA bart	4	2
	HbH/Hb pakse	0	2
	EA bart with CS	5	4
	HbH	1	0
Gender	Male/Female	14/27	20/25
Treatment pattern	Deferiprone monotherapy	23	22
	Deferoxamine monotherapy	4	6
	Combination	14	17
Duration of iron chelation therapy	More than 2 years	20	26
	2 years or less	21	19
Caregiver	Parent	35	38
	Grandparent	6	7
History of splenectomy		15	14
Serum ferritin	Less than 1000ng/ml	15	17
	1000-1500 ng/mL	15	14
	Greater than 1500 ng/ml	11	14

RESULTS

A total of 92 paediatric thalassemia patients were recruited at the start of the study. Six patients discontinued iron chelation therapy before completion of the study and were excluded leaving 86 patients. Most patients (n=48, 55.81%) were diagnosed with β-thalassemia/HbE (Table 1). Half of the patients had received iron chelation therapy for longer than 2 years (n = 46, 53.49%) and parents were the main care givers and responsible for drug administration (n = 73, 84.88%). There were 41 patients in the calendar group and 45 patients in the non-calendar group.Overall baseline demographics are shown in Table 1. The average age of patients was 12.29 years (SEM = 3.64) in the calendar group and 12.04 years (SEM = 3.98) in the non-calendar group. Forty-five patients received deferiprone (n = 45, 52.33%) or deferoxamine (n = 10, 11.63%) as a monotherapy and 31 patients (36.05%) received combination therapy. Most of the patients assessed their adherence to iron chelation therapy before the beginning of the study at the 'good' level. Most patients had baseline serum ferritin at 1500

ng/mL or less (30 patients in the calendar group (73.17%) and 31 patients in the non-calendar group (68.89%)).

Adherence to iron chelation therapy

Adherence to iron chelation therapy increased in both the calendar and non-calendar groups.In the calendar group, adherence to deferiprone increased by 3.03 % per visit for monotherapy (SEM = 0.49, P-value< 0.001, 95%CI 2.07:3.99) and by 2.17% per visit for combination therapy (SEM = 0.89, P-value = 0.015, 95% CI 0.42:3.92), while adherence to deferoxamine increased by 5.66% per visit for monotherapy (SEM = 1.45, P-value <0.001, 95% CI 2.82:8.49) and by 2.05% per visit for combination therapy (SEM = 0.97, P-value = 0.035, 95% CI 0.15:3.96). In the non-calendar group, deferiprone, adherence increased by 1.42% per visit (SEM =0.49, P-value = 0.005, 95%CI 0.44:2.39) for monotherapy and 2.20%per visit (SEM = 0.84, P-value = 0.008, 95% CI 0.56:3.84) for combination therapy. For deferoxamine, adherence increased by 3.92% per visit (SEM = 1.39, P-value = 0.005, 95% CI 1.20:6.64) for monotherapy, but the 0.31% (SEM = 0.89) per visit increase in adherence for deferoxamine in the combination therapy group was not significant (P-value = 0.727, 95% CI -1.44:2.05). A significant difference between the calendar and non-calendar groups in the per-visit increase in adherence was observed for deferiprone monotherapy (3.03%, SEM = 0.49 vs 1.42%, SEM = 0.49, respectively, P-value =0.008).

Subgroup analysis of adolescent patients (n = 45) showed similar results with adherence increasing in all groups, but to a lesser extent. For deferiprone monotherapy, adherence increased for the calendar group (2.51% per visit (SEM = 0.67), P-value <0.001, 95%CI 1.19:3.82) and the non-calendar group (2.29% per visit (SEM = 0.77), P-value =0.003, 95%CI 0.78:3.81), but the difference between groups was not significant. Adherence for deferiprone in combination therapy increased significantly in the non-calendar group (2.92% per visit (SEM = 1.08), P-value =0.007, 95% CI 0.82:5.03), but not in the calendar group (1.89% per visit (SEM = 1.22), P-value = 0.120, 95% CI 0.49:4.29). For deferoxamine, the calendar group showed a significant increase in adherence as monotherapy (5.14% per visit (SEM = 1.87), P-value = 0.006, 95%CI 1.48:8.80) and in combination (3.08% per visit (SEM = 1.50), P-value = 0.040, 95%CI0.14:6.02) but there were no significant increases in adherence for deferoxamine in the non-calendar groups(2.49% per visit (SEM = 1.87), P-value = 0.181, 95% CI 1.16:6.16, in monotherapy and 0.76% per visit (SEM = 1.29), P-value = 0.558, 95% CI 1.78:3.30 in combination therapy). There was a significant difference between the calendar and non-calendar groups in the increase in adherence for deferoxamine monotherapy (P-value =0.004).

The most common reason given for non-adherence (Table 2) was to forget to take the drug (n = 80, 93.02%). This was the major reason for non-adherence provided by patients receiving deferiprone monotherapy (97.78%), deferoxamine monotherapy (60%) and combination therapy (96.77%). Pain or irritation at the injection site was the second most common cause for non-adherence in patients receiving deferoxamine (21 of 41 patients, 51.22%).

Change of serum ferritin

A total of 81 patients were eligible for serum ferritin change analysis after 6 visits.The average serum ferritin level decreased by 20.25 ng/mL in the calendar group (SEM = 23.80, P-value = 0.394, 95% CI -66.92:26.38) and increased by 59.63 ng/mL in the non-calendar group (SEM = 23.01, P-value = 0.011, 95%CI 13.53:103.73). This difference was statistically significant (P-value = 0.015).

DISCUSSION

This study was conducted to evaluate the effect of a providing a drug use calendar to young thalassemia

Table 2. Reasons provided by young thalassemia patients for non-adherence to iron chelation therapy

Reason of non-adherence	**Frequency (%)**			
	Overall (n = 86)	**DFP (n = 45)**	**DFO (n = 10)**	**DFO/DFP (n = 31)**
Forgotto use medication	80(93.02)	44 (97.78)	6 (60)	30 (96.77)
No attention from parents when using medication	38(44.19)	17 (37.78)	4 (40)	17 (54.84)
Too busy to use medication at school	25(29.07)	14 (31.11)	1 (10)	10 (32.26)
Pain/irritation at injection site	21(51.22)*	N/A	7 (70)	14 (45.16)
Chose to not use medication	13 (15.12)	5 (11.11)	2 (20)	6 (19.35)
Not show-up for medication refill	7(8.14)	4 (8.89)	0	3 (9.68)
Reluctant to use medication in public	5 (5.81)	4 (8.89)	0	1 (3.23)
Insufficient injection devices	2 (4.88)*	N/A	1 (10)	1 (3.23)
Stopped using medication due to GI disturbance	2 (2.63)**	1 (2.22)	N/A	1 (3.23)
Skipped one medication of combination therapy	1 (1.16)	N/A	N/A	1 (3.23)

DFP = deferiprone, DFO=deferoxamine, DFO/DFP = combination therapy, N/A = no assessment, *calculated from deferoxamine use only, **calculated from deferiprone use only.

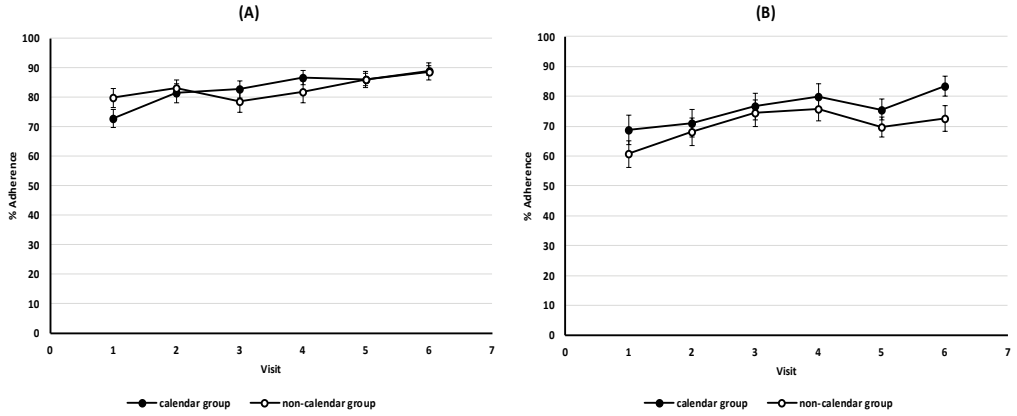

Figure 1. Adherence to deferiprone use in monotherapy group (A) and combination therapy group (B)

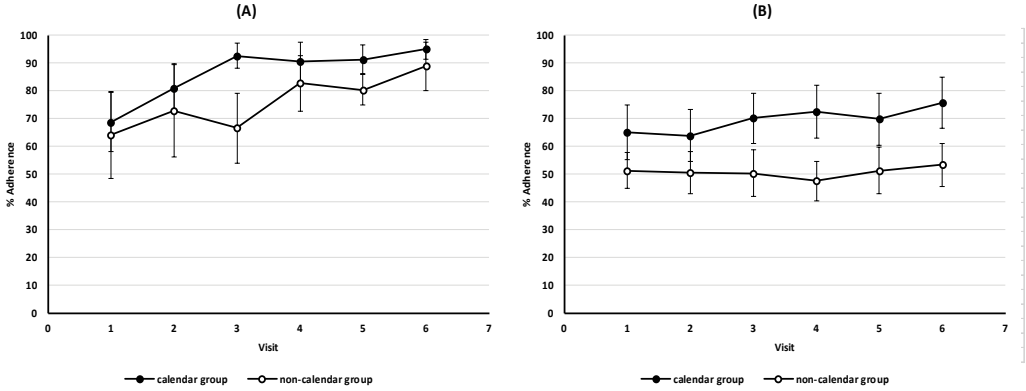

Figure 2. Adherence to deferoxamine use in monotherapy group (A) and combination therapy group (B)

patients on adherence to iron chelating medications. The results show that, overall, patients provided with a calendar had significantly higher adherence to deferiprone as monotherapy and adolescent patients provided with a calendar had significantly higher adherence to deferoxamine monotherapy. The main reason given by patients and caregivers for non-adherence was that they forgot to use the medication, therefore providing them with a calendar containing their individual drug-use schedule could improve adherence. Although local site reactions following deferoxamine injection have been known to be an important cause of poor adherence for this drug,[9,10] this reason for non-adherence was less common than 'forget to use the drug' in the current study.As the interval of deferoxamine use is not regular; 5-7 days per week in monotherapy and 2-5 days per week in combination therapy, provision of a calendar with the drug use schedule could be a key contributing factor for the increased adherence to deferoxamine seen in the adolescent calendar group.

There were also significant improvements seen in adherence to iron chelators in the non-calendar groups, although the per visit increases were smaller.This might be caused by surveillance bias, which occurs in studies of this type, when the simple act of measuring adherence leads to a change in behaviour in the participants and an increase in adherence, as observed in the non-calendar group. This problem can be generally overcome by using a large number of participants, designing suitable controls, and employing a long study time. Given that a smaller magnitude increase in adherence was observed in the non-calendar group, the controls used and the nine-month duration of this study appeared to be sufficient to overcome problems of surveillance bias, and this did not solely contribute to the improved adherence in the calendar group. Increasing the population size may improve the ability of the statistical tests to discriminate between improvements in the calendar and non-calendar groups. Nevertheless, it can be assumed that the addition of a drug-use calendar to the regular standard pharmaceutical care can improve adherence to iron chelator therapies in young thalassemia patients.

Among young patients, adolescents are known to have age-specific problems with adherence due to the physical and emotional changes associated with adolescence.[16,17] Adolescents that suffer with chronic diseases may also struggle with maintaining their self-esteem and confidence, which may cause them to resist

using treatments, especially in public.[18] Adherence to deferoxamine monotherapy in adolescents improved in the calendar group in the current study. Furthermore, participants rarely reported reluctance to use medication in public as a cause of non-adherence for deferoxamine, suggesting that the increased adherence to deferoxamine use by adolescents in the calendar group in the monotherapy arm was related to calendar use. This is in line with data from a previous study indicating that 'feeling shy to take iron chelators in front of others'only slightly contributed to poor adherence in adolescents.[12] A vast array of technologies have been suggested as tools to improve drug adherence in young patients, but these technologies may not work well in countries where mobile phones are not allowed in classrooms, as in some schools in Thailand.[19,20] Drug use calendars represent a more appropriate low cost, simple and portable solution to improving drug use adherence in this situation.

There is a relationship between poor adherence to iron chelation therapy and iron overload in transfusion dependent thalassemia.[12] In the current study, while there was an improvement in adherence seen in both the calendar and non-calendar groups, the average serum ferritin level decreased in the calendar groups but increased in the non-calendar group. This clearly indicates the potential for positive outcomes in thalassemia treatment that can come from incorporating a calendar of drug use into standard care for young thalassemia patients.

The participants were classified into groups before commencing the study according to their demographic characteristics and self-assessment of their adherence. However, the actual baseline adherence of patients used for data analysis was measured on V1 with pill and vial counts resulting in some variation in baseline adherence between groups. This necessitated using a multiple linear progression model for statistical comparison between the groups, rather than a simple direct comparison of adherence scores.

CONCLUSIONS

Young thalassemia patients and their caregivers said that forgetting to take medications was the major reason for non-adherence to iron chelation therapy. Provision of a drug use calendar increased adherence to deferiprone and deferoxamine and improved serum ferritin levels.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

DISCLOSURES

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