Factors Affecting Adherence of Beta-Thalassaemia Patients towards Iron Chelation Therapy in Hospital Keningau

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Abstract

Introduction: Survival in patients with beta-thalassaemia major is strongly influenced by adherence to iron chelation therapy (ICT). Studies showed that half of these patients die before the age of 35 due to poor adherence.

Objective: To determine ICT adherence level and thalassaemia disease knowledge level, the association between thalassaemia disease knowledge and ICT adherence level, and to explore the factors affecting the ICT adherence.

Method: A cross-sectional study was conducted over three months from May to July 2018 involving thalassaemia patients in Hospital Keningau. A combination of self-administered questionnaire and data collection form was utilised. The questionnaire comprised four sections: baseline demographics, Thalassaemia Disease Knowledge Assessment and factors affecting adherence to deferiprone and desferrioxamine. Data collection form was used to collect clinical data and for ICT adherence level assessment. Spearman Rho correlation test was used to examine the relationship between thalassaemia disease knowledge and ICT adherence.

Results: A total of 52 patients, predominantly female (n=31, 59.6%) with a median age of 17 years old (IQR=7.5) were included in the study. The median ICT adherence level was 87.5% (IQR=33.3), while 61.5% (n=32) of patients had moderate to good level of thalassaemia disease knowledge. No association was found between thalassaemia disease knowledge level and adherence (ρ= -0.124, p=0.396). Laziness (n=10, 25.6%) and pain at injection site (n=10, 25.6%) were the main reasons for poor adherence reported by patients on desferrioxamine, compared to laziness (n=12, 29.3%) and drug side effects (n=10, 24.4%) for deferiprone.

Conclusion: ICT adherence among thalassaemia patients was suboptimal despite moderate disease knowledge, with no significant association between knowledge and adherence. Non-adherence was mainly influenced by patient and treatment-related factors. Targeted, patient-centred interventions addressing these barriers are needed to improve adherence and optimise patient outcomes.

Keywords: Thalassaemia, adherence, knowledge, factor

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Introduction

Thalassaemia is one of the common inherited blood disorders (1). It interferes with the body's ability to produce haemoglobin, leading to chronic anaemia, physical complications, and a significantly reduced quality of life (2). Treatment varies depending on the type and severity of the disease. In thalassaemia major, regular packed red blood cell transfusions are essential for survival (3, 4). However, repeated transfusions lead to iron overload, which necessitates consistent iron chelation therapy (ICT) for survival. Without adequate chelation, cardiac failure becomes the leading cause of death in thalassaemia patients, accounting for up to 71% of deaths (5). Hence, long-term prognosis depends not only on transfusion but also on adherence to ICT (6).

Adherence to ICT in Malaysia remains a persistent challenge. A 2023 study reported adherence rates of estimated 20% for oral-only treatment and 47.5% for combined subcutaneous and oral regimens (7). The consequences of poor adherence are detrimental. Over 50% of patients die before the age of 35, mainly due to avoidable organ damage, significant morbidity and mortality, and poor health-related quality of life (8, 9). These outcomes occur despite the availability of effective therapy, suggesting that the issue lies not only with the treatment itself, but is a complex phenomenon influenced by behavioural, cognitive, and psychological factors that influence adherence to ICT (10).

A profoundly good disease knowledge, a major component in health literacy, has been suggested to directly influence a patient's ability to cope with their medical condition, engage with treatment, and make informed decisions (11). However, the impact of thalassemia disease knowledge on adherence to ICT presents a complex picture. Among patients receiving combined subcutaneous and oral ICT, those with lower knowledge scores were significantly more likely to be non-adherent (7). Conversely, another study reported that while low monthly household income was associated with poor adherence, there was no correlation between thalassaemia knowledge and adherence levels (12). These inconsistent findings highlighted the need for further research to determine whether knowledge level is directly associated with adherence behaviour, or whether this relationship is mediated by other psychosocial factors. Without such evidence, healthcare professionals lack the focused and practical strategies needed to improve long-term ICT adherence. Addressing this gap will provide valuable insights for planning more effective and sustainable thalassaemia care (13).

In 2020, Sabah reported the highest number of thalassaemia patients in Malaysia at 22.72% (5). A substantial number of these patients reside in remote and rural areas, particularly in the Keningau district. The thalassaemia disease knowledge level in these patients remains underexplored. Prior research among thalassaemia patients in Sabah often focused on patients residing in urban areas. Differences in cultural beliefs and health literacy levels between urban and rural populations may also contribute to differences in ICT adherence (4, 14). Furthermore, searching through published literature yielded no previous studies that have specifically investigated the factors influencing ICT adherence among patients in rural areas. Therefore, this study aimed to determine the ICT adherence level, thalassaemia disease knowledge level, the association between disease knowledge and ICT adherence level, and to explore factors affecting ICT adherence. This study addressed the following research questions: How much do thalassaemia patients from rural communities understand about thalassaemia? Does knowledge affect ICT adherence among thalassaemia patients in rural areas? What factors affect ICT adherence among these patients? Our study hypothesises that a higher level of thalassaemia disease knowledge level is associated with better ICT adherence. Upon completion, this study will provide a clearer understanding of thalassaemia disease knowledge and ICT adherence level within rural communities, forming a basis for formulating effective, patient-oriented thalassaemia care strategies.

Methodology

Study Design

This was a cross-sectional study conducted over a three-month period between May and July 2018 at the medical wards and Thalassaemia Day-Care Unit of Hospital Keningau. The Thalassaemia Day-Care Unit operates from Tuesday to Friday and is equipped with 11 beds for paediatric patients and 10 beds for adult patients. Patients typically attend for blood transfusion at the intervals of two to four weeks, depending on their haemoglobin levels. During each visit, their vital signs and weight are recorded, followed by pre-transfusion testing that include full blood count, blood grouping and cross-matching, as well as periodic liver and renal function tests and serum ferritin monitoring. In cases where thalassaemia patients develop significant anaemia or related complications, they are admitted to the medical ward for further management.

In our setting, desferrioxamine (DFO) is usually administered via subcutaneous continuous infusion using a portable pump over eight to 20 hours daily, for five to seven nights per week. Meanwhile, deferiprone (DFP) is administered orally in three divided doses daily (10). The average daily doses for DFO and DFP are 20–60mg/kg/day and 75–100mg/kg/day, respectively. As DFO and DFP were the most commonly prescribed ICT during the time of our study, they were selected as the therapies of interest for this study.

Study Population

All thalassaemia major patients who visited the Day-Care Unit for routine blood transfusions, and those who were admitted to the medical wards when complications arise were included in the study. During study commencement, there were only 72 registered thalassaemia patients in the hospital's registry. Therefore, no study sampling was carried out. Thalassaemia patients were recruited into the study if they were aged more than 12 years old, had regular follow-ups at the hospital, and were receiving ICT maintenance therapy (either DFO alone, DFP alone, or a combination of DFO and DFP). Patients were excluded if they were patients with neurological or psychological disorders or patients or caregivers who are unable to communicate in either Malay or English language.

Study Instrument

Data Collection Form

A data collection form was used to collect clinical data and for ICT adherence level assessment. The form consisted of three sections: Section A: Clinical Data, Section B: Adherence Assessment for Desferrioxamine, and Section C: Adherence Assessment for Deferiprone. For adherence assessment, study investigators asked patients to recall the actual dose and frequency of their medication taken at home. This information was then divided by the actual prescribed dose obtained from drug prescriptions (15). The calculated adherence level was between 0 (non-adherence) to 100% (adherence). The other clinical data in the data collection form was compiled by the pharmacist in charge of the medical wards or the Thalassaemia Day-Care Unit.

Self-administered Questionnaire

The self-administered questionnaire consisted of four sections: Section A: Patient baseline characteristics, Section B: Disease Knowledge Assessment, Section C: Factors affecting adherence to desferrioxamine, and Section D: Factors affecting adherence to deferiprone.

Section B: Disease Knowledge Assessment was adapted from the Disease Knowledge about Thalassaemia Major (DKTM) questionnaire (13). Permission to use the questionnaire was granted by the author. The original 20-item DKTM questionnaire was reviewed by an expert panel comprising two medical specialists and three senior pharmacists from the Thalassaemia Medication Therapy Adherence Clinic (TMTAC). The panel members independently reviewed all items for suitability, practicality, and relevance to the local context. Based on their evaluation, particularly considering the differences in perception and literacy between urban and rural populations, the final questionnaire adapted for our study consisted of ten items with either "Correct (*Betul*)" or "Wrong (*Salah*)" response options.

Subsequently, the questionnaire was translated into Malay language, and the accuracy of the translation was verified through back-translation by two language experts. To ensure face validity, a pilot study involving five patients was conducted to ensure that there were no conflicting and confusing terms and the sentences were simple and easy to understand.

Each item in the questionnaire was scored as 0 (for incorrect answers) or 1 (for correct answers). The total score ranged from 0 to 10 (maximum score), which was then converted to a percentage score from 0 to 100. Percentage scores below 50% were classified as poor disease knowledge, scores between 60% to 70% as moderate disease knowledge, and scores above 80% as good disease knowledge (16, 17).

For Section C and D, the factors affecting adherence to DFO and DFP were pre-identified based on literature reviews, clinical observations, and suggestions from the paediatricians (3, 4). Fifteen factors affecting adherence were identified for DFO, while twelve factors were identified for DFP. Patients were also asked to choose one most important factor affecting their own ICT adherence based on the type of ICT they received. If a patient received a combination of DFO and DFP, the patient had to answer both Section C and Section D.

Data Collection Procedure

Patients who met the inclusion criteria and exclusion criteria were approached, and written informed consent was obtained from the patients or their caregivers prior to data collection. All required data in this study were collected using a self-administered questionnaire and data collection form.

For adherence assessment, study investigators asked patients to recall the actual dose and frequency of their medication taken at home, and recorded the information in the data collection form. Then, the patients were asked to fill in the self-administered questionnaire. If any terms were unclear or confusion arose, patients may approach the study investigators for clarification. Study investigators would ensure that the questions were fully understood prior to patients' responses. To minimise bias in data collection, the study investigators were briefed on the data collection procedures and study terms definition to ensure standardisation, complete understanding, and consistency throughout the data collection process.

Ethics Approval

This study was registered with the National Medical Research Register (NMRR) and approved by the Ministry of Health Medical Research and Ethics Committee (MREC) with reference number NMRR-18-404-39581 (IIR).

Data Analysis

The data were analysed using Statistical Package for the Social Sciences (SPSS) version 20. Categorical data were presented in frequency and percentage, while continuous data were presented as mean and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for skewed data. Due to non-normally distributed characteristics, the Spearman Rho correlation test, a non-parametric analysis, was used to examine the relationship between thalassaemia disease knowledge and ICT adherence level. A *p* value of less than 0.05 was considered as statistically significant. Responses on factors affecting adherence were analysed descriptively.

Results

During the study period, a total of 72 patients were registered in the Thalassaemia Hospital Registry. Of these, 16 patients were no longer under follow-up and 4 patients had passed away. All the remaining 52 patients received ICT therapy, hence, 52 patients (72.2%) met all the inclusion criteria and were included in this study. Among these patients, 38 (73.1 %) received combined therapy, while remaining patients were treated with either DFO (n=5, 9.6%) or DFP (n=9, 17.3%) as monotherapy.

The baseline characteristics of the patients were summarised in Table 1. Patients were predominantly female (n=31, 59.6%), with median age of 17 years old (IQR= 7.5). Most patients (76.9%) were still attending school or pre-university, while the remaining 21% were not in school. The median monthly household income was RM500 (IQR=650). The median duration of journey from home to the hospital by any motorised vehicle was approximately 0.7 hours (IQR=0.7).

Table 2 summarised the median ICT adherence level assessment, with three missing data points reported for combined ICT. The overall median adherence level was 87.5% (IQR=33.3). Table 3 summarised the thalassaemia disease knowledge assessment scores among thalassaemia patients in Hospital Keningau. The detailed responses of the thalassaemia disease knowledge assessment were presented in Supplementary File 1. Overall, the median thalassaemia disease knowledge score was 60% (IQR=30). In our study, 61.5% of patients scored at least 60% and above in the disease knowledge assessment, while 20 patients (38.5%) scored ≤50%.

The relationship between thalassaemia disease knowledge and ICT adherence level was summarised in Table 4. There was no statistically significant relationship between thalassaemia disease knowledge and ICT adherence level with (ρ= -0.124, p=0.396).

Table 1: Baseline characteristics of patients (n=52)

Variables	Response received	Frequency, n (%)	Median (IQR)
Gender			
Male	52	21 (40.4)	
Female		31 (59.6)	
Age (years)	52		17 (7.5)
Household income (RM, monthly)	28		500 (650)
Highest education level			
No	51	11 (21.2)	
Primary School		12 (23.5)	
Secondary School		27 (52.9)	
Pre-University		1 (1.9)	
Duration from home to hospital (hours)	48		0.7 (0.7)
Iron chelation therapy			
(DFO+DFP)	52	38 (73.1)	
DFO		5 (9.6)	
DFP		9 (17.3)	
Splenectomy			
No	51	37 (72.6)	
Yes		14 (27.5)	
Long term antibiotics			
No	50	37 (74)	
Yes		13 (26)	
Family history of thalassaemia			
No	50	18 (36)	
Yes		32 (64)	
Eye examination			
No	51	29 (56.9)	
Yes		22 (43.1)	
Auditory examination			
No	51	32 (62.8)	
Yes		19 (37.3)	
Pneumococcal vaccination			
No	48	40 (83.3)	
Yes		8 (16.7)	
Serum ferritin (mcg/ml)	52		6102.5 (8885.1)

Abbreviation: SD = standard deviation, RM = Ringgit Malaysia, DFO = Desferrioxamine, DFP = Deferiprone, IQR = Interquartile Range

Table 2: ICT adherence level assessment (n=49)

Iron Chelation Therapy	Frequency, n	Adherence, %, median (IQR)
Iron Chelation Therapy		
Combination (DFO+DFP)	35	80 (33.5)
DFO	5	100 (0)
DFP	9	100 (33.3)
Overall	49	87.5 (33.3)

Abbreviation: DFO = Desferrioxamine, DFP = Deferiprone, IQR = Interquartile Range

Table 3: Thalassaemia disease knowledge assessment scores (n=52)

Category of Assessment Score	n (%)
≤ 5 (≤ 50%)	20 (38.5)
6 - 7 (60-70%)	18 (34.6)
8 - 10 (80-100%)	14 (26.9)

Abbreviation: IQR = Interquartile Range

Table 4: Spearman Rho correlation test between thalassaemia disease knowledge score and ICT adherence level

Variables	Frequency, n	ρ	p-value
Knowledge - Adherence	49	-0.124	0.396

Abbreviation: ρ= Spearman Rho

Figure 1 demonstrated the reported factors contributing to poor adherence to DFO, based on a total of 39 responses. The most frequently reported reasons were pain at injection sites such as phlebitis (n=10, 25.6%), laziness (n=10, 25.6%) and the unavailability of syringe pumps and fear of side effects (n=4, 10.3%, respectively). For DFP, a total of 41 responses were received. The most reported factors affecting adherence were laziness (n=12, 29.3%), the side effects experienced (n=10, 24.4%), and pill burden (n=7, 17.1%), as shown in Figure 2.

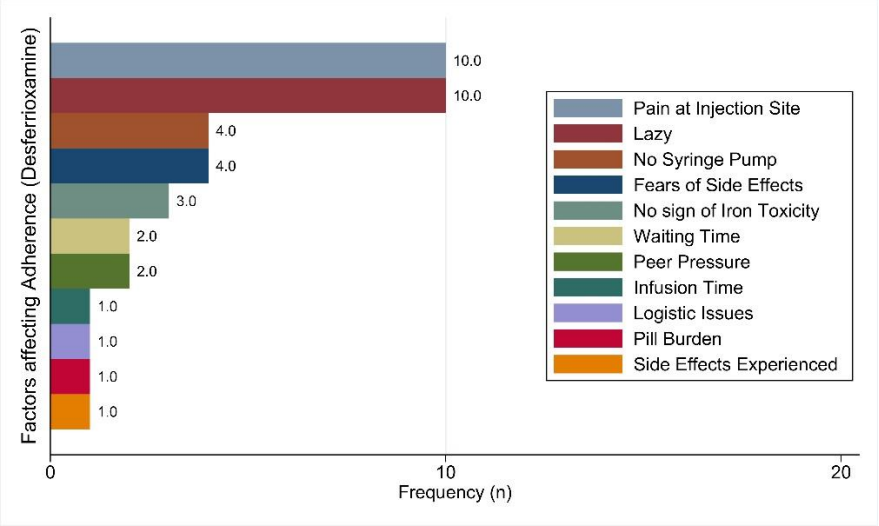

Figure 1: Factors affecting adherence to Desferrioxamine (n=39)

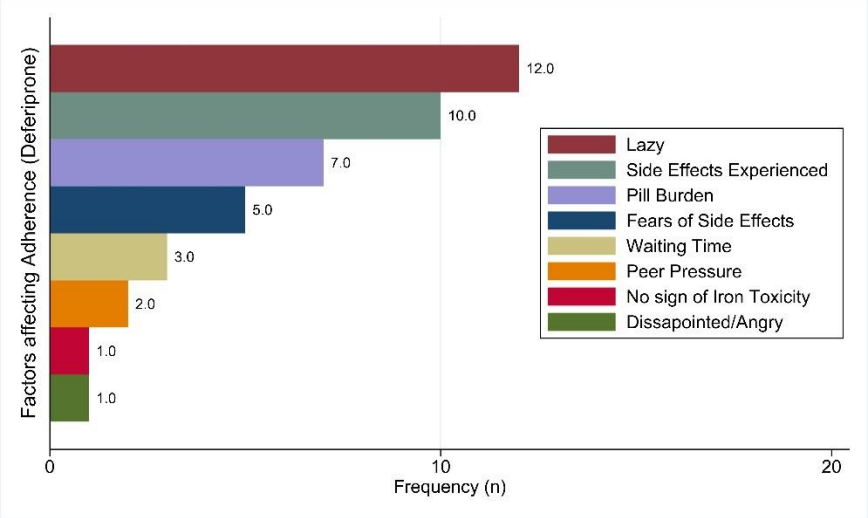

Figure 2: Factors Affecting Adherence to Deferiprone (n=41)

Discussion

Adherence to ICT remains a critical determinant of optimal clinical outcomes in transfusion-dependent thalassaemia patients. In our study, ICT was predominantly administered as combination therapy among the 52 included patients, with only a minority receiving desferrioxamine or deferiprone as monotherapy. Combination therapy is often introduced in patients who remain inadequately chelated on monotherapy; however, our findings demonstrate notable differences in adherence between regimens (18). Adherence was high among patients receiving monotherapy, whereas those on combination therapy exhibited comparatively lower adherence. This trend aligned with previous reports suggesting that more complex regimens, particularly those requiring multiple daily doses or simultaneous administration of different chelators, are more difficult for patients to adhere to (8, 19). The lower adherence observed in combination therapy underscored the practical challenges faced by patients in managing intricate treatment schedules. It further highlighted the need for interventions that simplify therapy and provide additional support to ensure consistent administration (20).

Disease knowledge is widely recognised as a key component in promoting self-management and adherence among patients with chronic conditions, including thalassaemia (13). In this study, while a substantial proportion of patients possess adequate knowledge about thalassaemia and its management, a significant subset demonstrated limited understanding. This knowledge gap may impair patients' ability to fully engage in effective self-care, recognise the importance of consistent ICT, and make informed treatment decisions. This highlighted the need for targeted educational interventions, particularly for younger patients or those from lower socioeconomic backgrounds, to strengthen disease literacy and support long-term treatment success (20).

Despite its importance, our analysis revealed no significant correlation between disease knowledge and adherence to iron chelation therapy, suggesting that higher knowledge scores may not necessarily translate into better adherence. This finding is consistent with studies by Al-Kloub et al. and Mohamed et al., both of which similarly reported no association between thalassaemia knowledge and treatment adherence among adolescent patients, a population comparable to ours (12, 16). Conversely, other studies have reported a weak but significant positive relationship between disease knowledge and adherence. Alnaami et al. found that patients with a greater understanding of their disease were more likely to follow their treatment plans, a perspective supported by Moustafa et al., who emphasised the need for educational strategies for patients and caregivers to improve adherence (17, 21). Together, these findings suggested that while understanding the disease is important, knowledge alone is often insufficient to overcome practical and behavioural barriers to consistent therapy. Prior research confirmed that adherence is more strongly influenced by factors such as regimen complexity, treatment-related side effects, and patient motivation rather than disease knowledge alone (8, 12). This underscored the need for multifaceted interventions that not only educate patients but also address real-world challenges, provide psychosocial support, and simplify therapy regimens to improve adherence and clinical outcomes.

In both treatment groups, laziness was reported as a factor affecting adherence in more than 50% of patients. Laziness, a patient-related factor, was also identified by Chong et al. as a result of emotional distress or negativity associated with thalassaemia, as well as difficulties in integrating the time-consuming medication regimen into daily routines (4). Participants in their study reported using avoidance coping strategies to manage these challenges and stressful situations, particularly during periods of low haemoglobin (4). The difficulty in integrating the medication regimen into daily routines may be attributed to the restrictions on physical activities imposed by both the severe disease condition and the treatment regimen involving desferrioxamine. As reported by Chat Chai et al., desferrioxamine therapy is particularly challenging due to its long infusion duration, which can significantly disrupt daily routines (10). Furthermore, activity restriction is a key component of quality-of-life assessments. The study by Trachtenberg et al. found that impaired quality of life, resulting from such restrictions, was associated with poor adherence with ICT (22).

Fear and concerns regarding the side effects associated with ICT are more prevalent among Asian patients compared to White patients (22). Patient-related factors such as laziness and fear of side effects can be addressed through several strategies, including the Three-Factor Interventional Model and Attachment Theory (20). Both approaches emphasise the importance of a strong, collaborative relationship between patients and clinicians. By integrating the patient's individual

concerns, beliefs, and motivations into the decision-making process, these strategies promote mutual understanding and facilitate the development of practical disease management goals and expectations. At our hospital, the Thalassaemia Medication Therapy Adherence Clinic (TMTAC), provided by pharmacists, offers counselling services designed to enhance patient adherence through personalised support, education, and guidance on effective medication management.

Other noteworthy factors affecting adherence in our patients include pain during desferrioxamine infusion and side effects experienced by patients on deferiprone, such as nausea, vomiting, and diarrhoea. Pain or irritation at the injection site was also reported by 51% of participants in another study, making it the second most common reason for non-adherence to ICT (23). Additionally, a study found that 91.7% of patients made errors during desferrioxamine administration, with most errors occurring during the dilution process (24). Using a more concentrated solution may cause irritation during injection, but this risk can be mitigated through proper preparation. Patients should be educated about the common side effects and practical management strategies, especially at the beginning of treatment. This approach helps to manage patients' expectations, address concerns, and foster trust and active participation in disease management. Patients are encouraged to report side effects so that they can be addressed by clinicians during visits, which helps to minimise intentional non-adherence.

If therapy-related factors remain intolerable despite the strategies outlined above, a change in therapy may be considered. In Sabah, desferrioxamine was the most commonly prescribed iron chelator, followed by deferasirox, which is predominantly used in paediatric patients, while combination therapy with desferrioxamine and deferiprone was introduced in 2018. Deferasirox, a newer once-daily iron chelator, may mitigate several barriers to adherence, including infusion-site pain, pill burden, and complex dosing regimens. Some formulations are available as dispersible tablets, facilitating administration in children. Its simplified dosing schedule has been associated with improved adherence compared to deferiprone (22). A meta-analysis by Qadah reported that deferasirox was comparable in efficacy to desferrioxamine, supporting its use as an alternative in patients who experience difficulty in adhering to other iron-chelating regimens (25).

There were a few limitations in our study. Firstly, there was a possibility of recall bias, especially with questions about adherence. Patients were asked to recall the number of times they have taken or injected their medications over the past week, and inaccuracies in their recollection or omission of details could lead to inaccurate data and adherence percentages. Secondly, the potential for misinterpretation of certain questions may have affected the reliability of the responses. Lastly, our study population was limited to patients who are 12 years old and older. Consequently, the findings may not be generalisable to younger paediatric patients, who often depend more heavily on parental oversight for disease management.

Conclusion

This study found that adherence to ICT among patients with thalassaemia remains suboptimal, despite a moderate level of disease knowledge. The absence of a significant association between thalassaemia knowledge and ICT adherence suggested that knowledge alone is insufficient to drive optimal treatment behaviour. Instead, practical and patient-related factors may play a more critical role in influencing adherence. These findings highlighted the need for a more comprehensive and patient-centred approach to improve ICT adherence, focusing not only on education but also on addressing behavioural, psychological, and treatment-related barriers. Interventions such as enhanced patient support, side effect management, improved access to administration devices, and regimen simplification should be considered. Ultimately, the insights from this study can guide healthcare professionals in developing targeted, effective, and sustainable care strategies to optimise adherence and improve clinical outcomes among patients with thalassaemia.

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Conflict of Interest Statement
No external funding was received and the authors declared no conflict of interest.

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Supplementary Data

Results of Thalassaemia Disease Knowledge Assessment (n=52)

	Correct answer	Responses			
		Correct *(Betul)*		Wrong *(Salah)*	
Thalassaemia adalah sejenis penyakit genetic *(Thalassaemia is a genetic disease)*	Correct	29	55.7%	23	44.2%
Setiap pesakit thalassaemia memerlukan rawatan transfusi darah *(Each patient with thalassaemia needs blood transfusion treatment)*	Wrong	51	98.1%	1	1.9%
Suntikan *Desferal*© adalah untuk menyingkirkan serum ferritin berlebihan dan untuk mengelakkan pengumpulan ferritin serum *(The reason for Desferal© injection is to get rid of excess serum ferritin and to avoid serum ferritin sedimentation)*	Correct	50	96.2%	2	3.8%
Punca bengkak hati dan limpa adalah disebabkan oleh kemusnahan sel darah merah yang berlebihan *(The cause of swelling of the liver and spleen is attributed to rapid destruction of red blood cell)*	Correct	30	57.7%	22	42.3%
Apabila pankreas bengkak / radang, ia akan menyebabkan kencing manis *(Once the pancreas is swollen/ inflamed, it will cause diabetes)*	Correct	12	23.1%	40	76.9%
Kadang-kala doktor mencadangkan untuk mengeluarkan limpa pesakit supaya dapat mengelakkan kemusnahan sel darah merah dengan cepat *(Sometimes doctor suggest removing the patient's spleen to avoid rapid cell destruction)*	Correct	45	86.5%	7	13.5%
Tahap hemoglobin harus dikekalkan melebihi 10g/dL untuk pesakit thalassaemia *(The level of haemoglobin should be maintained above 10g/dL in patients with thalassaemia)*	Correct	32	61.5%	20	38.5%
Jika kedua-dua ibu bapa adalah pembawa thalassaemia, maka kesemua anak yang dilahirkan akan menghidapi thalassaemia *(If both parents are the carriers of thalassaemia, all their children will be born with thalassaemia)*	Wrong	31	59.6%	21	40.4%
Tahap normal bagi serum ferritin adalah di bawah 1000mcg/L *(The normal range of serum ferritin levels is less than 1000mcg/L)*	Correct	31	59.6%	21	40.4%
Diet untuk pesakit thalassaemia adalah makanan yang mengandungi zat besi yang rendah *(The diet for thalassaemia patient should be low in iron)*	Correct	3	5.8%	49	94.2%