Iran Red Crescent Med J. 2018 April; 20(4):e60820. doi: 10.5812/ircmj.60820.

Published online 2018 April 20. **Research Article**

The Effect of a Holistic Care Program on the Reduction of Iron Overload in Patients with Beta-Thalassemia Major: A Randomized Clinical Trial

Mahdieh Arian [1], Robabeh Memarian [2,*], Mohammad Bagher Oghazian [3], Farveh Vakilian [4] and Zahra Badiee [5]

[1] Nursing Care Research Center, Semnan University of Medical Sciences, Semnan, IR Iran
[2] Nursing Department, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, IR Iran
[3] Department of Internal Medicine, Faculty of Medicine, North Khorasan University of Medical Sciences, Bojnurd, IR Iran
[4] Atherosclerosis Prevention Research Center, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, IR Iran
[5] Department of Pathology, Mashhad University of Medical Sciences and Health Services, Mashhad, IR Iran

[*] *Corresponding author*: Robabeh Memarian, Nursing Department, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, IR Iran. Tel: +98-2182883899, Fax: +98-2182884555, E-mail: memari_r@modares.ac.ir

Received 2017 September 06; **Revised** 2017 October 20; **Accepted** 2017 November 18.

Abstract

Background: The increased iron load is the main problem in beta-thalassemia major; chelation therapy is used for its counteraction. Non-compliance with iron chelation therapy leads to certain complications and the economic burden caused by them further highlights the importance of therapies for reducing iron overload. Administering lower doses of the chelating agent reduces both the complications faced by the patients and the economic burden on the health system.

Objectives and Methods: This randomized clinical trial was conducted to investigate the effect of a holistic care program (HCP) on the reduction of iron overload in patients with beta-thalassemia major referring to the largest center for thalassemia patients in Mashhad (Iran). Ninety eligible patients were randomly selected and enrolled in this study from September 2012 to February 2015. The subjects gave their informed consent and were then divided into an intervention (n = 45) and control group (n = 45) through stratified randomization while taking into account the type of a chelating agent as the confounder. The HCP was conducted as a randomized trial in three parts: 1- individual counseling (4 45 - 60-min sessions for each patient), 2- group training (4 60 - 90-min sessions for each patient), and 3- rehabilitation (8 weeks). Of the 500 patients with beta-thalassemia major, 90 samples were randomly selected. After they gave their informed consent, the samples were randomly assigned to 2 groups, i.e., an HCP group and a control group. Before beginning the intervention and 3 months later, the patients' levels of serum ferritin and iron, total iron binding capacity or TIBC (to check the iron load), and hemoglobin or Hb (to prevent hemolysis) were examined and the 6-minute walk test (6MWT) was also performed for assessing their functional ability and to ensure they were able to comply with the rehabilitation program. The patients in the control group received routine care only. The pre- and post-intervention evaluations in the control group were similar to those in the intervention group.

Results: Changes in serum iron and ferritin, as well as the 6MWT distance, differed significantly between the test and control groups ($P < 0.05$). TIBC and Hb levels, however, showed no significant differences between the two groups ($P > 0.05$). The mean changes in serum iron and ferritin, 6MWT, TIBC, and Hb equaled -71.02 ± 97.28, -1172.75 ± 2032.14, 65.97 ± 81.1, 29.71 ± 80.95, and 0.06 ± 1.75 in the intervention group and -5.46 ± 96.73, -8.08 ± 998.56, -33.97 ± 54.28, 21.37 ± 90.45, and 0.33 ± 1.5 in the control group.

Conclusions: It seems that any change in the mental and psychological conditions of chronic patients, especially those with thalassemia, improves their self-care behaviors and thereby, their treatment compliance. Based on the results, the HCP was effective in reducing ferritin levels in patients with thalassemia major in this study. Therefore, this is program is recommended to be used in the care of thalassemia patients.

Keywords: Beta-Thalassemia, Ferritin, Holistic, Iron, Nursing

1. Background

Beta-thalassemia syndromes are a group of genetic blood disorders characterized by the reduced and/or deficient synthesis of the globin chain leading to a reduction in hemoglobin in red blood cells and ultimately anemia. The disease is more prevalent in the Mediterranean countries, the Middle East, Central Asia, India, Southeast China, the Far East and North African and South American countries (1). In the Eastern Mediterranean region, Iran is a major B-thalassemia endemic region. There are between 2 to 3 million thalassemia carriers and 25,000 tha-

lassemia patients in Iran (2). In the B-thalassemia major, chronic blood transfusion leads to iron overload due to ineffective hematopoiesis (3). Excess iron cannot be naturally removed from the body, and the effects and complications of iron overload are fatal if left untreated (4). The complications of iron overload include pituitary damage, growth disorders, glandular disorders such as diabetes, hypothyroidism, hypoparathyroidism, hypogonadism, cardiac complications, liver damage, fibrosis, and ultimately liver cirrhosis (5). Estimating serum ferritin levels is a predominant test that checks for iron overload in patients with B-thalassemia major, and maintaining a serum ferritin level of 1000 mg/L is the standard and recommended therapeutic goal for these patients. This level of ferritin is achieved after 10 - 12 blood transfusions and is the starting point for the administration of chelators for preventing further increase (6). The most important treatment known for reducing the iron load and preventing its resultant complications is the use of chelating agents (5). The complications of these agents at high doses cause problems for patients; for example, the subcutaneous injection of Deferoxamine (DFO) is time-consuming and painful, and the DFO should be injected within 8 to 12 hours (7). The drugs are sometimes administered at high- doses due to excessive iron overload and thus, result in cutaneous and allergic reactions, pulmonary and neurological complications, and ultimately failed to adhere to the treatment (8). Approved oral medications such as Deferiprone (DFP) are also associated with side-effects such as gastrointestinal complications, agranulocytosis, neutropenia, and elevated liver enzymes, which make treatment and compliance with the drug regimen strenuous in patients with liver damage and chronic hepatitis (9). As for other drugs, such as Exjade (Deferasirox or DFX), side effects such as increased creatinine, proteinuria, elevated liver enzymes, and problems with vision and hearing impede the continuation of treatment (10). In addition to the noted side effects, these drugs impose a considerably heavy economic burden on the health system in thalassemia-endemic regions. Researchers are therefore recommended to not only look for chelating agents, but also seek better care measures that help reduce both the incidence of complications in the patients and the economic burden on health systems by enabling the administration of lower doses of these agents (11). Given that thalassemia patients experience cardiac complications such as arrhythmias and heart failure to varying degrees, introducing care approaches with the least cardiac side-effects and the greatest impact on iron levels is crucial.

Molazem et al. (2016) investigated the effect of a planned care program on the iron load of 38 thalassemia major patients in Shiraz, Iran. Their results showed that serum ferritin levels decreased significantly ($P < 0.05$) in the intervention group, two months after the beginning of the intervention (12). Karl et al. (2010) examined the effect of a 9-week basic combat training (BCT) on the iron status of female soldiers and observed a reduction in the iron load (13). Auersperger et al. (2013) studied female runners with normal iron reserves to measure iron storage indices in long-term exercise and detected a reduction in iron levels that did not return to the baseline values within ten days (14). According to what was noted, thalassemia affects all the physical, spiritual, social, and spiritual aspects of the patient's life. In addition, since these dimensions are interconnected in every person, the therapeutic care team should not only focus on medication therapy and should design specific plans for thalassemia patients through standard care approaches and programs influencing all these aspects in addition to self-care.

A holistic care approach is recommended in the care of chronic patients because it focuses on supporting the patient's body, mind, spirituality, community, emotions, and needs. The uniqueness of each patient and their different conditions with others comprise a major principle in holistic care programs or HCP (15). This approach consists of two phases. The first phase concerns the program design with holistic principles and the guidance of experienced nurses and therapeutic care teams. At the design stage, the focus is on the principles of the holistic care, i.e., person, practice, recovery and health, nurses, and self-care. The second phase deals with the implementation of the program designed based on the process of holistic care. In some applications, however, an intermediate stage is also considered after program design or before program implementation, which is concerned with familiarizing the patients with the designers of the care program for probable modifications. Sometimes, the intermediate phase is combined with the implementation phase; however, the program will be more effective if it is taken separately. Positive care and nursing performance are critical in the implementation stage, i.e., the second phase (16). The variability of chronic transfusion complications, the different physical and mental conditions emerging in the patients, and the principles applied both to the design and implementation of the care program are the main reasons for choosing a holistic approach in designing the present care program.

2. Methods

2.1. Aim and Design

A randomized clinical trial was conducted to investigate the effectiveness of HCP in reducing the iron load in patients with B-thalassemia major admitted to Sarvar

Clinic in Mashhad (the largest clinic for thalassemia patients in Mashhad affiliated to Mashhad University of Medical Sciences in Iran), who were divided into an intervention and a control group. The study lasted from September 2012 to February 2015. The study protocol was approved by the ethics committee of Tarbiat Modares University, and the project was registered at the Iranian Registry of Clinical Trials (www.irict.ir) under the ID # IRCT2017010720326N2.

2.2. Study Outcomes

The primary outcomes of this trial included changes in serum ferritin and iron levels three months after the beginning of the intervention. The most significant complication in thalassemia major is iron overload, which can lead to complications and ultimately death. Fluctuations in serum ferritin and iron levels are essential in clinical trials investigating the thalassemia major (5, 12).

The secondary outcomes included changes in serum ferritin levels in both the first and the second years after the intervention. TIBC, 6MWT, and Hb also showed changes three months after the beginning of the intervention.

2.3. Eligibility

The study inclusion criteria were: individuals above the age of 18, residing in Mashhad, learnability, and self-care abilities. The exclusion criteria were: non-compliance with the care program, hospitalization for any reason, the incidence of cardiac complications or infectious diseases during the study that required immediate changes to the prescribed cardiac medications and chelating agents, psychological problems, participation in similar research programs over the past six months, and not consenting to participation in the study.

2.4. Recruitment

A sampling frame was prepared, since the health records of all the thalassemia patients (n=500) were available in the clinic.

2.5. Prescreening and Screening

The patients' health status, anthropometric characteristics (height, weight, and BMI), and cardiac examination results were fully scrutinized by the nursing team, a cardiologist, and hematologist. A total of 240 patients were selected based on the eligibility criteria.

2.6. Data Collection

The patients' demographic information and other disease- and treatment-related information were collected through interviews during the initial screening. Serum ferritin, hemoglobin, total Iron binding capacity (TIBC), and the six-minute walk test (6MWT) were measured in both the intervention and control groups before and three months after beginning the intervention.

2.7. Blood Collection and Processing

At the Sarvar clinic for thalassemia patients, blood sampling for the evaluation of serum ferritin is a routine test for patients with thalassemia major. For this test, blood samples (10 cc) were collected from the antecubital vein both before and after the intervention. Serum iron, ferritin, and TIBC were measured with a Q1 Diaplus kit. Hemoglobin was measured by a Sysmex cell counter. The blood samples were tested at Sarvar clinic laboratory by the same person in all the measurements.

2.8. The Six Minute Walk Test (6MWT)

The 6MWT is a standard test that was used to determine the patients' functional ability. This test provides information about the patient's ability to carry out the rehabilitation program. In the present trial, the 6MWT was used to ensure that the rehabilitation program's level was commensurate with thalassemia major patients. For performing the test, the patient was asked to walk with their usual steps in a measured path for 6 minutes. The distance traveled during the 6 minutes was then measured (17).

2.9. Masking

The laboratory staff and the 6MWT examiner were blinded to the participants' random assignment into groups.

2.10. Sample Size

This study determined the sample size using the Altman nomogram (18) and the results of a study by Vashtani et al. in 2009 (5).

Alpha (type I error) = 5%
Power (1 - beta) = 90%
Difference between the means in the 2 groups = 350
Population standard deviation = 555/5
Standardized difference = 1.2

$$sd = \frac{2\delta}{Q_d} = \frac{2\,(350)}{555.5} = 1.2 \quad (1)$$

The sample size was estimated as 56 overall and 28 per group. Considering the probability of attrition, the sample size was raised to 90 overall and 45 per group.

2.11. Randomization Process

A sampling frame was prepared for this study. Of all the samples examined (n = 500), 240 met the eligibility criteria. Based on the estimated sample size, 90 of the eligible subjects were randomly selected (with a table of random numbers). The subjects gave their informed consent and were then divided into an intervention group (n = 45) and a control group (n = 45) through stratified randomization (with a table of random numbers) while taking into account the type of chelators Agent as the confounder.

2.12. Intervention

2.12.1. Intervention Group

The HCP was performed for the patients in the intervention group for 8 weeks. Before beginning the intervention, the content of the program (counseling, training and rehabilitation) was prepared in a way to produce comprehensible educational material for patients with thalassemia major and was approved by a cardiologist and hematologist. The nurses who assisted the researcher in this study were also trained on the program. The approved content was then performed as a pilot study to resolve any deficiencies. The program was finally implemented in the intervention group in three sections: 1- individual counseling (4, 45 - 60-min sessions for each patient), 2- group training (4, 60 - 90-min sessions), and 3- rehabilitation (20 sessions). Box 1 and Table 1 (19) present the details of the HCP.

2.12.2. Control Group

The control group received the routine care provided at the clinic only for eight weeks.

2.13. Data Analysis

The Kolmogorov-Smirnov test was used to evaluate the normal distribution of the data. The study data were analyzed using Chi-square, Fisher's exact test, independent samples t-test, and paired sample t-test and the repeated measures ANOVA using SPSS Statistical Software version 16.0 (SPSS Inc., Chicago, I.L., USA). The significance level was set at 0.05. Intention-to-treat (ITT) method was used for analysis and Regression method was used as a strategy for solving the problem of any missing value in this study.

3. Results

Some of the patients (n = 15) were excluded from the study due to hospitalization, unwillingness to continue the program, infection, death, relocation to another city, and incomplete data. A total of 45 patients from the intervention group and 45 from the control group were included in the statistical analysis (Figure 1: The consort flow diagram). The demographic data and clinical conditions did not differ significantly between the two groups (P > 0.05). There were no significant differences between the two groups regarding iron overload complications and regular exercise (P > 0.05), as presented in Table 2.

Based on the results presented in Table 3, the intervention group's mean of serum ferritin and iron levels three months after beginning the intervention was significantly lower compared to before the intervention (P = 0.001 and P = 0.001, respectively), while the two parameters showed no significant changes in the control group (P = 0.706 and P = 0.96, respectively). Both the intervention and control groups showed significant changes in their mean 3 months after beginning the intervention 6MWT distances compared to before the intervention values (P < 0.05). The mean 3 months after beginning the intervention 6MWT distance reduced in the intervention group (P = 0.001) but increased in the control group (P = 0.001). The mean TIBC and Hb did not show significant differences after the intervention in the intervention group (P = 0.079 and P = 0.819, respectively) and in the control group (P = 0.209 and P = 0.142, respectively).

As shown in Table 4, the changes in serum iron and ferritin and the 6MWT distance differed significantly between the two groups (P = 0.002 and P = 0.001 and P = 001, respectively), however, the changes in TIBC and Hb were not statistically significant (P = 0.725 and P = 0.425, respectively).

Figure 2 depicts serum ferritin changes in the intervention and control groups on the four screening occasions. The ferritin-levels 1-4 indicate the level of ferritin, pre-intervention, three months, one year, and two years after the intervention, respectively. The results of the repeated measures ANOVA showed significant differences in the mean serum ferritin level on the different screening occasions (P = 0.01), while no significant differences were observed in this respect in the control group (P = 0.07). In the intervention group, before the intervention serum ferritin level differed significantly from the level obtained three months after beginning the intervention and one and two years after the intervention (P = 0.001 and P = 0.001, and P = 0.001 respectively). Serum ferritin level also differed significantly when measured three months after beginning the intervention and when measured two years later (P = 0.046). Overall, the changes in ferritin level followed a

Box 1. A Summary of the HCP for Reducing the Iron Load in B-Thalassemia Major Patients

Summary of the HCP
1- Individual Counseling
The individual counseling program systematically provided each patient with problem-solving mechanisms in the following four steps:
The 1st step was communication between the patient and the counselor, with the aim of building familiarity and trust between them
In the 2nd step, the counselor identified the root causes of the patient's various needs and problems through conversation and an in-depth interview with the patient
In the 3rd step, the counselor prioritized the identified solutions based on the patient's potential and level of cooperation and satisfaction
Counseling ended with the 4th step by expanding the patient's ability to understand the issues and presenting appropriate solutions
2. Group Training
The group training program was aimed at encouraging treatment adherence in the patients and covered the following items:
The importance of having an association for thalassemia patients, having identity cards, benefiting from the available medical facilities, and attending meetings and workshops related to the association
New methods of thalassemia treatment
The importance of regular blood transfusion, the use of regular chelation therapy, and the use of supplements according to the physician's instructions
The effect of chelating agents and the complications of not using them
The complications of iron overload
Timely visits for the monthly and annual screenings
No use of iron-rich foods, especially in the interval between two transfusions
Taking antioxidants such as Vitamin C and E
The importance of preventing infection after splenectomy and explaining the relationship between infection and iron overload, and offering strategies for preventing infection (4, 20).
3- Rehabilitation
The rehabilitation program included the following steps:
In this trial, the rehabilitation program was designed according to the Oxford Cardiac Rehabilitation Program, including eight weeks of walking (endurance exercise) along with stretching (resistance exercise) in 3 steps, i.e., warm-up, walking and cool-down (19).
One week after the familiarization step, the intervention group received training on the techniques and conditions for entering each session of the rehabilitation program
The patients were evaluated by the assisting nurses before and after each session of the rehabilitation program
To control the exercise intensity during the implementation of the program, the maximum heart rate was first measured according to the equation (220 - [Age in years] $\pm$ 10), and the target heart rate range was then determined using the Karvonen formula:
Karvonen Formula = [(Maximal Heart Rate - Resting Heart Rate) 50% and 85% + Rest Heart Rate], where the Heart Rate Reserve (HRR) was used for determining the HR of training (21).
A PM45 heart rate monitor was used to maintain heart rate during the exercises.

Table 1. The Aerobic Rehabilitation Program Protocol

Week	Warming Up, Gradually Increasing Heart Rate, min	Main Exercise, Walking Maintain Target Heart Rate, min	Cooling Down, Gradually Decreasing Heart Rate, min	Total Time, Gradually Increasing Heart Rate, min	Sessions a Week
1	5	10	5	20	2
2	5	10	5	20	2
3	7	15	7	30 $\approx$ 29	2
4	7	15	7	30 $\approx$ 29	2
5	10	20	10	40	3
6	10	20	10	40	3
7	13	25	13	50 $\approx$ 51	3
8	15	30	15	60	3

downward trend in the intervention group.

4. Discussion

The present clinical trial found decreased serum ferritin and iron levels in the thalassemia major patients in the intervention group after implementing the HCP consisting of counseling, training, and rehabilitation. Moreover, the post-intervention screening two years later showed a reduction in serum ferritin levels in the intervention group.

The counseling section of the HCP addressed the approaches to the improvement of care behaviors in psychological and mental aspects and also the means of coping with depression. Yang et al. (2001) conducted a study in

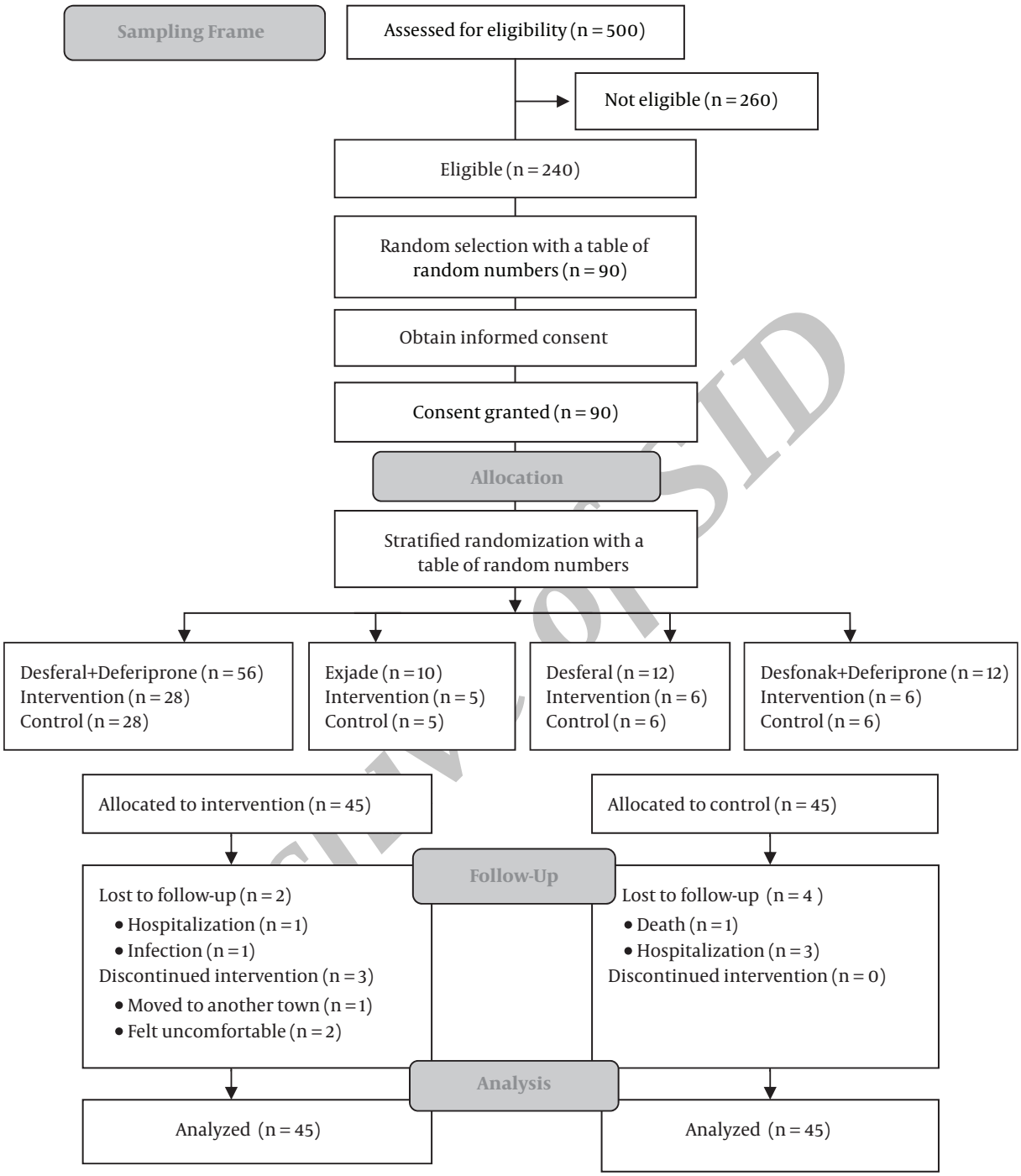

Figure 1. The Consort Flow Diagram

Taiwan and concluded that awareness about thalassemia and its complications, having social support, and participating in counseling programs are correlated with the adherence to chelation therapy in patients with thalassemia (22). It should be noted that an unpleasant physical image, delayed puberty, dependence on injection chelation therapy, frequent hospitalization, massive treatment costs and multiple physical complications are factors that sig-

Table 2. The Frequency Distribution of Demographic Variables, Time of Diagnosis, Chelator Agents, and Onset of Blood Transfusion in the 2 Study Groups[a,b]

Variable	Control Group, (n = 45)	Intervention Group, (n = 45)	P Value
Age group, y			0.083[c]
18 - 25	29 (64.4)	22 (48.9)	
26 - 30	12 (26.7)	19 (42.2)	
> 31	4 (8.9)	4 (8.9)	
Mean ± SD	23.91 ± 5.03	25.58 ± 3.92	
Gender			0.832[d]
Female	21 (46.7)	19 (42.2)	
Male	24 (53.3)	26 (57.8)	
Education level			0.499[e]
Elementary school	3 (6.7)	-	
Middle school	4 (8.9)	4 (8.9)	
High school	10 (22.2)	11 (24.4)	
Diploma	15 (33.3)	18 (20)	
Academic	13 (28.9)	12 (26.7)	
Marital status			0.192[d]
Single	40 (88.9)	36 (80)	
Married	5 (11.1)	9 (20)	
BMI	19.51 ± 2.26	19.75 ± 2.55	0.631[c]
Time of diagnosis, mo			0.229[e]
1 - 6	10 (22.2)	8 (17.8)	
7 - 12	16 (35.6)	24 (53.3)	
> 13	19 (42.2)	13 (28.9)	
Median (Q3 - Q1)	12 (13 - 8)	12 (20 - 8)	
Transfusion intervals, d			0.887[e]
14 - 20	5 (11.1)	6 (13.3)	
21 - 30	35 (77.8)	33 (73.3)	
> 31	5 (11.1)	6 (13.3)	
Median (Q3 - Q1)	25 (30 - 21)	21 (30 - 21)	
Number of packed red cells units at each visit			
1 - 2	39 (86.7)	34 (75.6)	0.281[d]
≥ 3	6 (13.3)	11 (24.4)	
Median (Q3 - Q1)	2 (2 - 2)	2 (2 - 2)	
Chelator agent			
Desferal	6 (13.3)	6 (13.3)	Matched
Exjade	5 (11.1)	5 (11.1)	
Desferal + Deferiprone	28 (62.2)	28 (62.2)	
Desfonak + Deferiprone	6 (13.3)	6 (13.3)	
Having a regular exercise program			0.408[d]
Ok	14 (31.1)	12 (26.7)	
No	31 (68.9)	28 (73.3)	

[a] Values are expressed as No. (%).
[b] Significance level: 0.05.
[c] Independent samples t-test.
[d] Fisher's exact test.
[e] Chi-square test.

nificantly affect the mental health of thalassemia patients, and lead to depression and non-compliance with treatment (20). During the individual counseling and group training sessions, the care team (cardiologist, hematologist, psychiatrist, and the nurse) regularly monitored and sought to meet the patients' needs and followed-up on their conditions to refer them to a psychiatrist for professional counseling, if needed.

Table 3. A Comparison of the Mean Iron Indices and Hb and 6MWT in the Study Groups Both Before and After the Intervention[a,b]

Variables	Control Group			Intervention Group		
	Before the Intervention	Two Months After the Intervention	P Value[c]	Before the Intervention	Two Months After the Intervention	P Value[c]
Serum iron, μg/dL	144.46 ± 87.22	139 ± 74.34	0.706	204.02 ± 100.95	133 ± 63.52	0.001
Ferritin, mg/L	2347.33 ± 1853.44	2355.4 ± 1607	0.96	3053.93 ± 2391.88	1881.18 ± 1178.65	0.001
TIBC, μg/dL	144.75 ± 57.82	166.13 ± 93.26	0.209	154.155 ± 92.31	183.86 ± 101.63	0.079
Hb	8 ± 1.54	8.33 ± 1.13	0.142	8.68 ±1.03	8.74 ± 1.51	0.819
6MWT	417.82 ± 102.9	383.84 ± 89.02	0.001	370.96 ± 90.78	436 ± 105.066	0.001

Abbreviations: SD, standard deviation; TIBC, total iron binding capacity; 6MWT six- minute walk test.
[a]Values are expressed as mean ± SD.
[b]Significance level: 0.05.
[c]Paired-sample t-test.

Table 4. A Comparison of the Changes in the Iron Indices in the Study Groups Both Before and After the Intervention[a]

Variables	Control Group Changes	Intervention Group Changes	Differences Between the Groups		
			95% Confidence Interval	Mean Differences	P Value[b]
Serum iron, μg/dL	-5.46 ± 96.73	-71.02 ± 97.28	(-106.199, -24.911)	-65.555	0.002
Ferritin, mg/L	-8.08 ± 998.56	-1172.75 ± 2032.14	(-1851.61, -510.07)	-1180.84	0.001
TIBC, μg/dL	21.37 ± 90.45	29.71 ± 80.95	(-38.46, +55.13)	8.33	0.724
Hb	0.33 ± 1.5	0.06 ± 1.75	(-0.96, +0.408)	-0.27	0.425
6MWT	-33.97 ± 54.28	65.97 ± 81.1	(69.03, +130.87)	99.95	0.001

Abbreviations: SD, standard deviation; TIBC, total iron binding capacity; 6MWT six- minute walk test.
[a]Significance level: 0.05.
[b]Independent sample t-test.

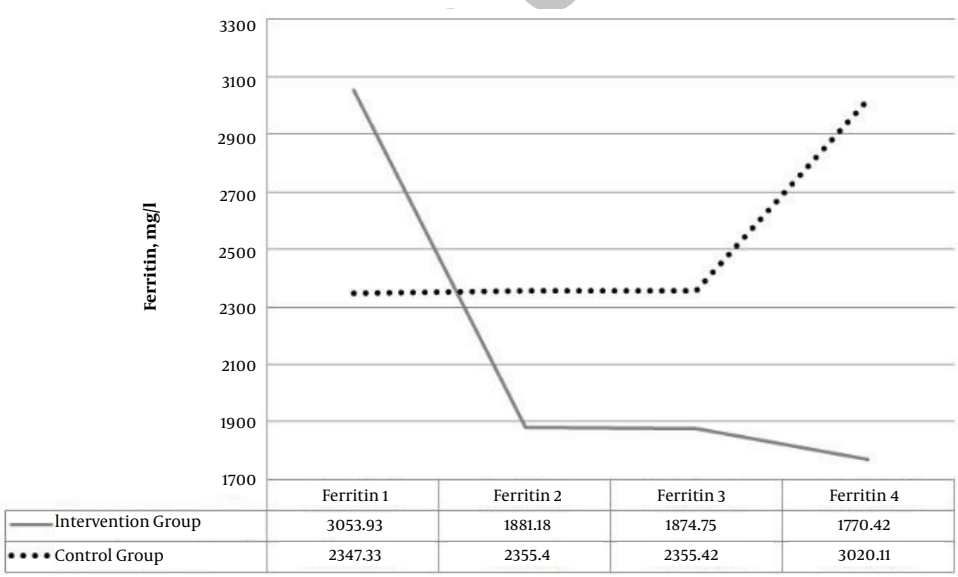

Figure 2. Depicts Serum Ferritin Changes in the Intervention and Control Groups on the Four Screening Occasions.

Any change in the mental status of chronic patients, especially those with thalassemia, leads to an improvement in self-care behaviors and compliance with the treatment. The training part of the HCP provided face-to-face and written training to increase awareness about the importance of proper nutrition, compliance with the treatments (including chelation therapy) and making timely visits for transfusion. A study by Lee et al. (2009) demonstrated that only 43% of patients are aware of the importance of regular blood transfusion and chelation therapy adherence, and

thus concluded that the patients' low level of knowledge is an important cause of their poor compliance with chelation therapy and other treatments. Therefore, they found a significant positive correlation between the patients' level of knowledge about thalassemia and their adherence to chelation therapy and blood transfusion (23).

Although intestinal iron absorption is not high in these patients and transfusion is the most common cause of iron overload in them, a low-iron diet is recommended for these patients (24). In patients with regular transfusions, hepcidin concentrations are markedly higher than in those with no transfusions. Hepcidin concentration decreases in the interval between two transfusions and rises again after each transfusion (25). In the intervals when Hepcidin drops, the intestinal absorption of iron also rises, and thalassemia patients undergoing regular transfusion should receive effective training to minimize the intestinal absorption of iron in the intervals between the two transfusions (24).

The 6MWT was used as the exercise part of the HCP for the purpose of rehabilitation and to assess the functional ability of the patients. The 6MWT distance increased in the intervention group after the intervention, which is consistent with the results obtained by Gary et al. in 2004 (26). Studies by Sheth (2014), Kampe (1998), Haymes (1989), Lamanca (1988), Modell (1983), and Weaver (1992) attribute the reduction in serum ferritin to exercise and believe that the serum ferritin reduction following intravascular hemolysis is involved in reducing the iron load (9, 27-31). These researchers have argued that intravascular hemolysis occurs after exercise; the present researchers monitored the hemoglobin level at regular intervals to ensure that the hemolysis administered was safe. Given the principled design and implementation of the program in this study, which took account of thalassemia patients' ability and particular conditions, no changes were observed in hemoglobin levels, and the need for blood transfusion did not decrease in the patients.

Another hypothesis related to the reduction of serum iron holds that iron release increases from the tissues after exercise and leads to serum iron overload after entering the bloodstream (27, 32). It should be noted that Desferal can help the body to excrete iron only when the iron is in the bloodstream and the Desferal binds to iron and its derivatives, and excretes them. In case there is no iron in the bloodstream, Desferal circulates in the blood without exerting any effects and is ultimately excreted (27). Since the patients were trained on the importance of adherence to chelation therapy and using Desferal, more iron must have been excreted from the body following the regular injection of Desferal. Despite the reduction in iron levels following the intervention, no increase was observed in TIBC in the intervention group, which is not consistent with the results obtained by Vashtani et al. in 2009 (5). However, it agrees with the results obtained by Molazem et al. in 2016 (12).

4.1. Limitations

All the stages of the HCP were conducted at the Sarvar clinic in Mashhad. The control group was studied in the morning shift when the clinic was more crowded, and the intervention group was studied and underwent the rehabilitation program in the evening, when the clinic was less crowded.

4.2. Conclusions

Any changes in the mental state of chronic patients, especially patients with thalassemia, appear to help improve self-care behaviors and consequently adherence to treatment. The results obtained suggest that the HCP approach used in this study has effectively reduced ferritin levels in patients with thalassemia major and is recommended to be further used in the care of thalassemia patients.

Acknowledgments

The authors would like to express their gratitude to the staff of Sarvar clinic, the Thalassemia Association of Khorasan Razavi province, and all the participants. This article has been extracted from a dissertation thesis approved by the faculty of medical sciences, Tarbiat Modares University, Tehran, in 2012 (ID 522080/d), registered at the Iranian registry of clinical trials under the ID IRCT2017010720326N2.

References

1. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis*. 2010;**5**:11. doi: 10.1186/1750-1172-5-11. [PubMed: 20492708].
2. Rezaee AR, Banoei MM, Khalili E, Houshmand M. Beta-Thalassemia in Iran: new insight into the role of genetic admixture and migration. *ScientificWorldJournal*. 2012;**2012**:635183. doi: 10.1100/2012/635183. [PubMed: 23319887].
3. Kurtoglu AU, Kurtoglu E, Temizkan AK. Effect of iron overload on endocrinopathies in patients with beta-thalassaemia major and intermedia. *Endokrynol Pol*. 2012;**63**(4):260–3. [PubMed: 22933160].
4. Mishra AK, Tiwari A. Iron overload in Beta thalassaemia major and intermedia patients. *Maedica (Buchar)*. 2013;**8**(4):328–32. [PubMed: 24790662].
5. Vashtani SH, Nazem F, Bordar F. The effect of aerobic rehabilitation program on concentration of ferritin, iron, TIBC and cardiovascular operation in the young patients suffering from major thalassemia. *J Guilan Univ Med Sci*. 2009;**18**(71):95–102.
6. Donovan A, Lima CA, Pinkus JL, Pinkus GS, Zon LI, Robine S, et al. The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. *Cell Metab*. 2005;**1**(3):191–200. doi: 10.1016/j.cmet.2005.01.003. [PubMed: 16054062].

7. Nisbet-Brown E, Olivieri NF, Giardina PJ, Grady RW, Neufeld EJ, Sechaud R, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet*. 2003;**361**(9369):1597–602. doi: 10.1016/S0140-6736(03)13309-0. [PubMed: 12747879].
8. Delea TE, Edelsberg J, Sofrygin O, Thomas SK, Baladi JF, Phatak PD, et al. Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. *Transfusion*. 2007;**47**(10):1919–29. doi: 10.1111/j.1537-2995.2007.01416.x. [PubMed: 17880620].
9. Sheth S. Iron chelation: an update. *Curr Opin Hematol*. 2014;**21**(3):179–85. doi: 10.1097/MOH.0000000000000031. [PubMed: 24504090].
10. Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, et al. Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. *Haematologica*. 2008;**93**(5):741–52. doi: 10.3324/haematol.12413. [PubMed: 18413891].
11. Ganz T. Hepcidin and iron regulation, 10 years later. *Blood*. 2011;**117**(17):4425–33. doi: 10.1182/blood-2011-01-258467. [PubMed: 21346250].
12. Molazem Z, Noormohammadi R, Dokouhaki R, Zakerinia M, Bagheri Z. The Effects of Nutrition, Exercise, and a Praying Program on Reducing Iron Overload in Patients With Beta-Thalassemia Major: A Randomized Clinical Trial. *Iran J Pediatr*. 2016;**In Press**(In Press). doi: 10.5812/ijp.3869.
13. Karl JP, Lieberman HR, Cable SJ, Williams KW, Young AJ, McClung JP. Randomized, double-blind, placebo-controlled trial of an iron-fortified food product in female soldiers during military training: relations between iron status, serum hepcidin, and inflammation. *Am J Clin Nutr*. 2010;**92**(1):93–100. doi: 10.3945/ajcn.2010.29185. [PubMed: 20444958].
14. Auersperger I, Skof B, Leskosek B, Knap B, Jerin A, Lainscak M. Exercise-induced changes in iron status and hepcidin response in female runners. *PLoS One*. 2013;**8**(3). e58090. doi: 10.1371/journal.pone.0058090. [PubMed: 23472137].
15. Erickson HL. Philosophy and theory of holism. *Nurs Clin North Am*. 2007;**42**(2):139–63. v. doi: 10.1016/j.cnur.2007.03.001. [PubMed: 17544676].
16. Frisch C. *AHNA Standards of Holistic Nursing Practice: Guidelines for caring and healing*. Jones & Bartlett Learning; 2000.
17. Arian M, Memarian R, Vakilian F, Badiei Z. Effects of a designed walking program on mental health, functional ability and Cardiac symptoms on Patients with thalassemia major. *Evid Base Care*. 2013;**3**(2):17–26.
18. Noordzij M, Tripepi G, Dekker FW, Zoccali C, Tanck MW, Jager KJ. Sample size calculations: basic principles and common pitfalls. *Nephrol Dial Transplant*. 2010;**25**(5):1388–93. doi: 10.1093/ndt/gfp732. [PubMed: 20067907].
19. Oxford center. *Cardiac rehabilitation exercise program*. Blackbird Leys Leisure center, Oxford Rad cliff Hospital; 2012. p. 5–6.
20. Cappellini MD, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. nd R, editor. *Guidelines for the clinical management of thalassaemia*. Nicosia (CY); 2008.
21. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. *Ann Med Exp Biol Fenn*. 1957;**35**(3):307–15. [PubMed: 13470504].
22. Yang HC, Chen YC, Mao HC, Lin KH. [Illness knowledge, social support and self care behavior in adolescents with beta-thalassemia major]. *Hu Li Yan Jiu*. 2001;**9**(2):114–24. [PubMed: 11548457].
23. Lee YL, Lin DT, Tsai SF. Disease knowledge and treatment adherence among patients with thalassemia major and their mothers in Taiwan. *J Clin Nurs*. 2009;**18**(4):529–38. doi: 10.1111/j.1365-2702.2007.02150.x. [PubMed: 19192002].
24. Nemeth E. Hepcidin in beta-thalassemia. *Ann N Y Acad Sci*. 2010;**1202**:31–5. doi: 10.1111/j.1749-6632.2010.05585.x. [PubMed: 20712769].
25. Abboud S, Haile DJ. A novel mammalian iron-regulated protein involved in intracellular iron metabolism. *J Biol Chem*. 2000;**275**(26):19906–12. doi: 10.1074/jbc.M000713200. [PubMed: 10747949].
26. Gary RA, Sueta CA, Dougherty M, Rosenberg B, Cheek D, Preisser J, et al. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart Lung*. 2004;**33**(4):210–8. [PubMed: 15252410].
27. Kampe CE, Rodgers GP, Oswalt JD, Sandbach JF. Exercise-induced fragmentation hemolysis: a simple in vivo test to evaluate heart valve hemolysis. *South Med J*. 1998;**91**(10):970–2. [PubMed: 9786297].
28. Haymes EM, Spillman DM. Iron status of women distance runners, sprinters, and control women. *Int J Sports Med*. 1989;**10**(6):430–3. doi: 10.1055/s-2007-1024938. [PubMed: 2628362].
29. Lamanca JJ, Haymes EM, Daly JA, Moffatt RJ, Waller MF. Sweat iron loss of male and female runners during exercise. *Int J Sports Med*. 1988;**9**(1):52–5. doi: 10.1055/s-2007-1024978. [PubMed: 3366520].
30. Modell B, Berdoukas V. *The clinical approach to thalassaemia*. New York; 1983.
31. Weaver CM, Rajaram S. Exercise and iron status. *J Nutr*. 1992;**122**(3 Suppl):782–7. [PubMed: 1542048].
32. Tavazzi L, Mortara A. Exercise training and the autonomic nervous system in chronic heart failure. *Eur Heart J*. 1995;**16**(10):1308–10. [PubMed: 8746894].