

Effect of multidimensional intervention on improving adherence of thalassemic children to iron chelation therapy

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Abstract

Background: Thalassemic patients' survival is closely linked to the quality of blood transfusion and iron chelation therapy. Non-adherence to chelation therapy severely compromises patient health, quality of life and survival. **Aim of the study:** Was to evaluate the effect of multidimensional intervention on improving adherence of thalassemic children to iron chelation therapy. **Subject and method: Research design:** A quasi experimental (pre-post) design was used. **Setting:** Pediatric Hematology Outpatient Clinic at Zagazig University Hospital, Zagazig, Egypt. **Subjects:** A purposive sample of 50 thalassemic children. **Tools of data collection:** Three tools were used to collect the necessary data included; a structured interview questionnaire, Morisky 8-Item Medication Adherence Scale (MMAS-8), and Chelation Therapy Management Form. **Results:** It was found that thalassemic children' adherence to iron chelation therapy and their serum ferritin levels were significantly improved after implementation of the multidimensional intervention (P=0.001). **Conclusion:** The multidimensional intervention improved thalassemic children' adherence to iron chelation therapy. **Recommendations:** multifaceted/ multidimensional interventions tailored to individual patients' needs, will be helpful in managing medication adherence issues.

Keywords: Adherence; Iron chelation therapy; Thalassemia; Multidimensional Intervention

Introduction:

Thalassemias are the most common genetic disorders that result from imbalance in the synthesis of globin chains⁽¹⁾. In β -thalassemia, reduced β globin production, leads to excess free α globin chains resulting in ineffective erythropoiesis, severe anaemia and bone marrow hyperplasia⁽²⁾. Both transfusion-dependent, and non-transfusion-dependent patients, are exposed to iron overload either as a result of regular red blood cells transfusion or increased intestinal iron absorption⁽³⁾. Iron overload can lead to iron toxicity because excess unbound iron cumulates in organs and can be converted to free radicals that damage the lipid membrane, proteins and DNA. Injury to these tissues may result in hepatic, endocrine, cardiac and joint toxicities^(4,5).

Iron chelating agents are used for preventing and treating iron overload⁽⁶⁾. Without iron chelation therapy, death from iron-induced heart failure occurs by the mid-teenage years in regularly transfused patients⁽⁷⁾. Thalassemic patients' adherence to chelation therapy usually influenced by the demanding nature of the

therapy, its uncomfortable side effects as well as its impaction on patient's daily activities, well-being and quality of life⁽⁸⁾.

Adherence is "the active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result."⁽⁹⁾. Adherence to iron chelation therapy decreases acute care needs and inpatient costs. Also, it reduces the financial burden on health programs and managed care plans treating thalassemic patients⁽¹⁰⁾. Patient, medication, health care providers, health care system and socioeconomic factors should be considered in creating suitable and individualized interventions to overcome non-adherence⁽¹¹⁾. Because medication adherence has various complex aspects, multifactorial solutions⁽¹²⁾ or a combination of various adherence improving techniques should be implemented to manage patient's adherence to their prescribed treatment⁽¹³⁾.

Significance of the study:

Iron overload requires lifelong chelation therapy and patient attitude

toward adherence will change over time. Non-adherence is a very serious matter, which may lead to serious or fatal complications that include hepatic fibrosis and cirrhosis, growth failure, diabetes mellitus, hypogonadotropic-hypogonadism, hypothyroidism, hypoparathyroidism, cardiomyopathies, and joint toxicities. Investing time, effort and resources in strategies to improve adherence will result in significant long-term benefits. As the success of chelation therapy, in terms of reduced morbidity and improved survival, is dependent upon good adherence.

Aim of the study:

The present study was conducted to evaluate the effect of multidimensional intervention on improving adherence of thalassemic children to iron chelation therapy.

The objectives of the study were to:

1. Assess adherence of children with thalassemia to their iron chelation therapy regimen.
2. Plan and implement the multidimensional intervention that includes: simplifying the regimen, imparting knowledge, modifying patient beliefs about medications, providing communication and trust, leaving the bias and evaluating adherence.
3. Evaluate the effect of the multidimensional intervention on improving thalassemic children' adherence to iron chelation therapy.

Research hypothesis:

Thalassemic children' adherence to iron chelation therapy will be improved after implementation of the multidimensional intervention.

Subjects and methods:

Research design:

A quasi experimental (pretest-posttest) design was used in carrying out the present study.

Study setting

The present study was conducted at Pediatric Hematology Outpatient Clinic at Zagazig University Hospital.

Study subjects:

The study was conducted on a purposive sample of 50 thalassemic children who accepted to participate in

the study and fulfilled the following criteria:-

- Age: from 10 to 18 years
- Serum ferritin level ≥ 1000 $\mu\text{g/ml}$
- Range of strategies for iron chelation: deferasirox, deferoxamine, deferiprone

A sample of 50 children with thalassemia was required to estimate an average change at adherence rate for iron chelating therapy after applying multidimensional intervention = 23% with estimated effect size of 0.3, using alpha error = 0.05 and dropout rate = 10% will provide a power of 80%.

Tools of data collection:

Three tools were used to collect the necessary data included; a structured interview questionnaire, Morisky 8-Item Medication Adherence Scale (MMAS-8) and Chelation Therapy Management Form.

Tool I: A structured interview questionnaire

A structured interview questionnaire was developed by the researchers after reviewing relevant scientific literature and articles in periodicals to collect the required data. It consisted of two main parts:

Part 1: Characteristics of the studied thalassemic children:

This part of the questionnaire concerned with : (children' characteristics, medical history of the disease, data about blood transfusion and data about iron chelation therapy.

Part 2: Factors affecting thalassemic children' adherence to iron chelation therapy

Tool II: Morisky 8-Item Medication Adherence Scale (MMAS-8)

Adherence to chelation therapy was measured by using the eight-item Morisky Medication Adherence Scale ⁽¹⁴⁾. The scale was translated into Arabic by the researchers. The MMAS-8, contains eight questions, seven closed ended questions with (yes/no) answers and the last question being answered according to a scale of five options: never/rarely, once in a while,

sometimes, usually and all the time. Each item of the scale (MMAS-8) measures a specific adherence behavior. Each yes answer will be given a score of 1 and no answer will be given a score of 0. For the last questions never/rarely will be given a score of (0) and once in a while, sometimes, usually and all the time will be given a score of (1) then the total score will be interpreted as >2 = low adherence 1 or 2 = medium adherence 0 = high adherence

Tool III: Chelation therapy management form

Chelation therapy management form was developed by the researchers and consisted of three parts as follows:

Part 1:

In this part the details of patients' old chelation regimen and the new simplified one were recorded by the researcher. This part included drug name(s), dose, route, frequency and daily time of taking the drug in both old and new modified regimens.

Part 2: Patient diary

It is developed by the researchers and guided by the diary designed by Pope⁽¹⁶⁾ It is composed of the following subparts:

First subpart: Patient's diary in which thalassemic children were asked to fill the following data related their chelation therapy every day (date, time of taking drug dose, whether he/she took his/her complete dose of iron chelator, the reason of not taking or completing the prescribed dose).

Second subpart: adherence rate was calculated and recorded every month during the intervention for a period of six months by the researcher through counting the bills of oral chelators or desferal vials by using the following equations: -

- Adherence rate (%) for oral chelators = (Number of pills taken) / (Number of pills prescribed) x 100.
- Adherence rate (%) for desferal = (Number of vials taken) / (Number of vials prescribed) x 100.

Part 3: Patient's serum ferritin level report

In this report serum ferritin levels were recorded for every thalassemic child three times throughout the study as follows; pre (before the intervention), post (immediately after the intervention) and follow-up (3 months later). These results were used as one of adherence evaluation methods (outcome measure).

The Multidimensional Intervention: - General objective of the multidimensional intervention

The multidimensional intervention aimed to improve adherence of thalassemic children to iron chelation therapy **through the following specific objectives: -**

1. Simplify chelation therapy regimen.
2. Impart knowledge about disease and treatment.
3. Modify patient beliefs about medication
4. Provide communication and trust
5. Leave the bias
6. Evaluate adherence

Content validity and reliability:

The tools were tested for content validity by five experts (two professors of pediatrics, one professor of maternal and newborn nursing, one professor of gerontology nursing and one professor of biostatistics). The recommended modifications were done and the final forms were ready for use. A reliability test was done for Morisky 8-Item Medication Adherence Scale (MMAS-8) and acceptable consistency was found with Cronbach's Alpha 0.791.

Field work:

The aim and the process of the study were explained and an oral consent was obtained from thalassemic children who accepted to participate in the study. The researcher interviewed thalassemic children individually to collect the necessary data and assess their adherence to chelation therapy. Then, the multidimensional intervention was implemented. The multidimensional intervention used in the present study was guided by Atreja et al. (2005)⁽¹⁷⁾, strategies to improve adherence which identified by what he called a mnemonic acronym, SIMPLE. These strategies were applied in a parallel way throughout the study by implementing some specific interventions as follows;

1. Simplify chelation therapy regimen

At the beginning of the study and after the initial assessment, the researcher met each child and his/her parents to discuss chelation therapy regimen and to identify if it was convenient to the child or not? Then, the researcher suggested a new modified regimen and discussed it with the child and his parents if the previous regimen was not convenient to the child. After that, the new modified regimen was discussed with the head of pediatric hematology/oncology unit. Then, through communication between the researcher and the child's physician the new modified regimen was done.

The suggested modifications to chelation regimen included; changing the iron chelator, adjusting time, frequency, amount, and sometimes dosage as well as matching the chelation therapy regimen to patients' activities of daily living. The details of patients' old chelation regimen and the new simplified one were recorded by the researcher in patient's chelation therapy management form.

Modifications of the chelation therapy regimen were done for patients who had problems with the suggested regimen and also on Ramadan to adjust the time of chelation doses to Iftar and Suhoor.

2. Imparting knowledge

Written information in the form of brochures which contained knowledge about the disease, treatment, chelation therapy and its importance, adverse effects of the chelation agents and its management as well as instructions about how to take the medication was given to all the studied thalassemic children. Patients were divided into groups according to their follow-up visiting schedule. Each group contained 5-7 thalassemic children. Duration of the educational session was (45-60 minutes). (Only one educational session was given for each group throughout the intervention)

3. Modifying patient beliefs

Patient fears, concerns and problems in taking iron chelators were addressed and handled through open discussion between patient and researcher at each visit. Patients perceived barriers in taking iron chelators were also addressed and handled by suggesting simple solutions to things that prevent thalassemic children from taking their chelation therapy e.g., being away from home, had too many pills to take, wanted to avoid side effects, felt like the drug was toxic/harmful, did not want other to notice you taking medication,.....etc. Small gifts were given to the studied children as a reward for their adherence to chelation therapy and for filling their diaries. The educational session was also helpful in handling some fears and concerns related to side effects of iron chelators and emphasizing on its importance, so it help in modifying patients' beliefs.

4. Patient and family communication

Regular meetings were conducted at each follow up visit to discuss patient and family fears and concerns as well as answering their questions about chelation regimen. Involving patients in decisions was done through discussing each thalassemic child about the new modified chelation therapy regimen -as mentioned before- and any modification was done according to patient preferences and adjusted to his daily living activities. The researcher called every studied

child by telephone once weekly throughout the study period to remind and encourage them to take their iron chelators and complete their diaries. Electronic messages were also sent via Facebook and What Sapp if available.

5. Leaving the bias

Educational sessions and brochures as well as any discussions or instructions given to the child or his family were tailored to patients' level of understanding.

6. Evaluating adherence was done through

Indirect Methods: -

Patient's diary was checked at every follow-up visit to the clinic. Pill counting and calculating adherence ratio was done every month as mentioned before. Medication Adherence Scale [Morisky-8 (MMAS-8)] was used to assess adherence to chelation therapy before and after the intervention.

Outcome Measures: -

Serum ferritin level was recorded three times throughout the study; before, after the intervention and three months later. The reduction in serum ferritin levels was used as an indicator of adherence with chelation therapy.

The researcher attended the Pediatric Hematology Outpatient Clinic four days/week (Saturday, Sunday, Tuesday, and Wednesday) for data collection and implementation of the multidimensional intervention. Data was collected during 9 months, starting from December 2015 to August 2016.

Pilot study:

A pilot study was conducted on 5 thalassemic children to test applicability, feasibility and practicality of the tools. No modification was done to the tools; accordingly the five children who shared in the pilot study were included in the study sample.

Administrative and ethical considerations:

An official permission for data collection was obtained by submission of an official letter issued from the director of the faculty of nursing at Zagazig University to the director of Out-Patient Clinics Hospital then to the head of Pediatric Hematology and Oncology unit at Zagazig University Hospital. Thalassemic children had been informed about the purpose and process of the study and an oral consent

was obtained from those who accepted to participate in the study. The researcher provided assurance of maintaining anonymity and confidentiality of patients' data, and emphasized on the patient's right to withdraw from the study at any phase.

Statistical Analysis:

The collected data was coded and entered to the SPSS version 19.0 program by which the analysis was conducted by using frequency tables with percentages and cross tabulations. Mc-Nemar test for related samples (P) was used to assess if there was a statistically significant change in thalassemic children' adherence to chelation therapy before and after the intervention by using Morisky 8-Item Medication Adherence Scale. Marginal Homogeneity test (H) was used to determine whether the level of thalassemic children adherence to their chelation is significantly changed after the intervention (difference between three rating categories low, medium and high adherence). Repeated measures ANOVA (F) was used to test the statistically significant difference in mean scores of adherence rate and serum ferritin levels throughout the study. Pearson correlation coefficient (r) was used to find the correlation between total score of Morisky scale, adherence rate and serum ferritin level. P value was statistically significant at < 0.05 and highly statistically significant at < 0.001.

Results:

Table 1 shows characteristics of the studied thalassemic children, their adherence to iron chelation therapy and causes of non-adherence. The results of the present study showed that mean age of the studied thalassemic children was 15.2 ± 2.3 years. Males composed 56% of the studied sample. It was also found that 58% of the studied children used deferiasirox for iron chelation. Health insurance provides regular access to treatment for 98% of the studied thalassemic children. In addition, 76% of the studied thalassemic children did not adhere to chelation therapy. Forget taking medication and being away from home were the most common things that prevent the studied children from taking their iron chelation therapy reported by 59.2% and 52% of them respectively.

Effect of multidimensional intervention on thalassemic children' adherence to their iron

chelation therapy regimen (Morisky 8-item medication adherence scale) was described in **table 2**. There was a statistically significant improvement in thalassemic children's adherence to their chelation therapy after implementation of the intervention (post phase) ($P=0.001$). As evidenced by increased "no" response in all items of the scale during post phase except item (no.5) in which "yes" response increased from 38% in pre phase to 86% in post phase and this is when the studied children were asked, "Did you take all your medicines yesterday?" that also reflects improvement in adherence.

Table 3 represents the total score of Morisky 8-item medication adherence scale. As observed from this table, the percentage of the studied children with low adherence score decreased from 86% before the intervention (pre) to 20% after the intervention (post). The difference was statistically significant ($H=15.9$ with $P=0.001$).

Adherence rate among the studied thalassemic children throughout the study was clarified in **table 4**. The overall mean of adherence rate of studied children was $78.2\% \pm 26.2\%$ with no statistically significant change throughout the intervention.

Table 5 describes the effect of multidimensional intervention on the studied thalassemic children's serum ferritin levels. The mean of serum ferritin level decreased from 4623.9 ± 3043.1 $\mu\text{g/ml}$ before intervention to 3992.1 ± 2786.5 $\mu\text{g/ml}$ after intervention then to 3536.7 ± 2653.3 $\mu\text{g/ml}$ at follow up phase with statistically significant difference. ($F=37.9$ with $P=0.001$).

Discussion:

The results of the present study revealed a statistically significant improvement in thalassemic children's adherence to their chelation therapy after implementation of the intervention. The percentage of adherent children increased from 14% before the intervention to 80% after the intervention. In a randomized clinical trial conducted to test a multifaceted intervention to improve adherence to cardiac medications, Ho et al. ⁽¹⁸⁾ supported the previous findings as they found statistically significant difference in adherence between the intervention group and the usual care group. Insel et al. ⁽¹⁹⁾ also agreed with the results of the present study, and reported a significant improvement in adherence in the intervention group (57% at baseline to 78% after the

intervention). Upon the previously mentioned findings either in the current study or other studies it can be concluded that, multidimensional or multifaceted interventions are effective in improving adherence to medications. This may be due to the fact that adherence is a multifaceted issue and to address it health care provider must manage the multiple factors surrounding it through effective interventions.

Regarding to adherence rate that was calculated and recorded by the researcher every month during the intervention for a period of six months, it was found that, the overall mean of adherence rate of studied children was $78.2\% \pm 26.2\%$ with no statistically significant change throughout the intervention. This adherence rate is slightly higher than self-reported adherence rate to chelation therapy (73%) by Jordanian thalassemic adolescents in Al-Kloub et al. ⁽²⁰⁾ study.

In the current study, small gifts were given to the studied children as a reward for their adherence to chelation therapy and for filling their diaries. These gifts helped in motivating the studied children to adhere to their chelation therapy. Moreover, there was a continuous evaluation of adherence through checking patient's diary at every follow-up visit to the clinic as well as, pill counting and calculating adherence rate was done every month. These measures helped in improving adherence rate and total adherence score of the studied thalassemic children. Atreja et al. ⁽¹⁷⁾ reported that, "regular assessment of patient adherence by itself can lead to increased patient adherence".

The ultimate goal of chelation therapy is a reduction in the body iron burden. Serum ferritin is a useful monitoring tool for iron overload in thalassemia major ⁽²¹⁾. So, the reduction in serum ferritin levels was used in the present study as an indicator of adherence with chelation therapy. The results of the present study revealed that, the mean of Serum ferritin level decreased from 4623.9 ± 3043.1 $\mu\text{g/ml}$ before intervention to 3992.1 ± 2786.5 $\mu\text{g/ml}$ after intervention then to 3536.7 ± 2653.3 $\mu\text{g/ml}$ at follow up phase with statistically significant difference. Despite statistically significant decrease in serum ferritin levels in the present study that reflect improved adherence, it still high and higher than serum ferritin levels reported by other

studies. Rofail et al. ⁽²²⁾, Pedram et al. ⁽²³⁾ and Rajish et al. ⁽²⁴⁾ reported lower serum ferritin levels respectively as follows; (2888±2247 µg/ml), (2000-4000 µg/ml), and (2000-4000 µg/ml). High serum ferritin levels in the current study could be explained in the light of its results. As the majority of the studied children had low adherence score before the intervention and when they were asked did you adhere to iron chelation therapy more than three quarters of them answered “no”. Also the base line of serum ferritin levels for the studied children was already high 4623.9±3043.1. Porter and Viprakasit⁽³⁾ reported that, iron chelation therapy should be started early before accumulation of toxic levels because it's very difficult to remove iron from the storage tissues so prevention is better than treatment.

In a study conducted to evaluate iron chelation therapy in thalassemia major patients at Zagazig University Hospital Badr et al. ⁽²⁵⁾ reported that, 21.3% of the studied thalassemic children had adherence rate less than 50%. In other two studies carried out at Zagazig University Hospital El-Dakhakhny et al. ⁽²⁶⁾ and Aboelela et al. ⁽²⁷⁾ found that, 58% and 80% of the studied thalassemic children respectively for both studies did not comply with iron chelation therapy. These findings were compatible with the low adherence that was found in the current study before the intervention. The most common findings that prevented the studied children from taking their iron chelation therapy were forgetfulness (59.2%), being away from home (52%), wanted to avoid side effects (51%), felt depressed/overwhelmed (49%), other priorities (42%) and unclear doctor's instructions (30%). Bosworth ⁽²⁸⁾ reported nearly the same reasons with different percentages as follows; forgetfulness (30%), other priorities (16%), deciding to omit a dose (11%), lack of information (9%), and emotional reasons (7%);

27% of patients give no reason. Zivin et al. ⁽²⁹⁾ reported that raised drug expenditures is a major cause of skipping pills and avoid filling prescriptions by patients in order to save cost. However, in the present study non-adherence was not related to cost as the cost of medication were covered by health insurance in nearly all the patients (98%).

Conclusion:

Thalassemic children adherence to iron chelation therapy and their serum ferritin levels were significantly improved after implementation of the multidimensional intervention.

Recommendations:

1. Multifaceted interventions tailored to individual patients needs would be helpful in managing medication adherence issues.
2. Continuous evaluation of patients' medication adherence and discussion of patients' beliefs and concerns about treatment regimen should be done at each visit to the clinic.
3. Conducting educational sessions and designing educational materials about disease, complications and treatment regimen tailored to patient's level of understanding are mandatory.
4. All health care providers must motivate thalassemic patients to comply with their treatment regimen. Providing small gifts for adherent young thalassemic children is very helpful in maintaining their treatment adherence.

Table 1: Characteristics of the studied thalassemic children, their adherence to iron chelation therapy and causes of non-adherence

Socio-demographic Data		No (n=50)	%
Age (years)	▪ 11-	11	22.0%
	▪ 13-	14	28.0%
	▪ 16-18	25	50.0%
Mean ± SD		15.2 ± 2.3	
Sex	▪ Male	28	56.0%
	▪ Female	22	44.0%
Iron chelating agents	▪ deferasirox	29	58.0%
	▪ deferiprone	10	20.0%
	▪ desferoxamine	2	4.0%
	▪ desferoxamine and deferasirox	2	4.0%
	▪ desferoxamine and deferiprone	1	2.0%
Adherence to iron chelation therapy	▪ Nothing	6	12.0%
	▪ No	38	76.0%
From your point of view; what are the most common things that prevent you from taking your iron chelation therapy or which cause you do not take some doses? ☺	▪ Yes	12	24.0%
	▪ Simply forget	29	59.2%
	▪ Being away from home	26	52.0%
	▪ Wanted to avoid side effects	25	51.0%
	▪ Felt depressed/overwhelmed	24	49.0%
	▪ Busy with other things	21	42.0%
	▪ Had too many bills to take	17	34.7%
	▪ Did not want other to notice you taking medication	15	30.6%
	▪ Had problem taking bills at specified times (with meals, on empty stomach, etc..)	15	30.6%
	▪ Doctor's instructions about taking medication were unclear	15	30.0%
	▪ Had a change in daily routine	14	28.6%
	▪ Fell asleep/slept through dose time	14	28.6%
	▪ Felt sick/ill	14	28.0%
	▪ Felt good	6	12.2%
	▪ Ran out of bills	2	4.1%
▪ Felt like the drug was toxic/harmful	1	2.0%	
Type of therapeutic support	▪ Health insurance	49	98.0%
	▪ Ministry of health	1	2.0%

SD: standard deviation, ☺ More than one answer.

Table 2: Effect of multidimensional intervention on thalassemic children' adherence to their iron chelation therapy regimen (Morisky 8-item medication adherence scale)

Morisky 8-Item Medication Adherence Scale		Phase				P
		Pre		Post		
		No (n=50)	%	No(n=50)	%	
1. Do you sometimes forget to take your medicine?	no	14	28.0%	45	90.0%	0.001*
	yes	36	72.0%	5	10.0%	
2. People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?	no	12	24.0%	36	72.0%	0.001*
	yes	38	76.0%	14	28.0%	
3. Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	no	26	52.0%	43	86.0%	0.001*
	yes	24	48.0%	7	14.0%	
4. When you travel or leave home, do you sometimes forget to bring along your medicine?	no	15	30.0%	41	82.0%	0.001*
	yes	35	70.0%	9	18.0%	
5. Did you take all your medicines yesterday?	no	31	62.0%	7	14.0%	0.001*
	yes	19	38.0%	43	86.0%	
6. When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	no	26	52.0%	48	96.0%	0.001*
	yes	24	48.0%	2	4.0%	
7. Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	no	17	34.0%	44	88.0%	0.001*
	yes	33	66.0%	6	12.0%	
8. How often do you have difficulty remembering to take all your medicine?	never	13	26.0%	44	88.0%	0.001*
	once in a while, sometimes, usually or all the time	37	74.0%	6	12.0%	

P: Mc-Nemar test for related samples

* P < 0.05 (significant)

Table 3: Total score of Morisky 8-item medication adherence scale

Total Medication Adherence score (Morisky 8-Item Medication Adherence Scale)	Phase				H (P)
	Pre		Post		
	No (n=50)	%	No (n=50)	%	
Low adherence	43	86.0%	10	20.0%	
Medium adherence	6	12.0%	37	74.0%	15.9 (0.001)*
High adherence	1	2.0%	3	6.0%	
Range	0-8		0-7		
Mean ± SD	4.9 ± 1.7		1.8 ± 1.6		

H: Marginal Homogeneity test, * P < 0.05 (significant), >2 = low adherence, 1 or 2 = medium adherence and 0 = high adherence, SD: standard deviation.

Table 4: Adherence rate among the studied thalassemic children throughout the study (during implementation of the intervention)

Adherence rate	Mean ± SD	Range	F (P)
First month	75.4% ± 32.6%	0% -100%	
Second month	74.8% ± 34.5%	0% -100%	
Third month	79.1% ± 31.7%	0% -100%	
Fourth month	78.1% ± 30.8%	0% -100%	0.85 (0.463)
Fifth month	81.0% ± 30.5%	0% -100%	
Sixth month	81.0% ± 32.7%	0% -100%	
Overall	78.2% ± 26.2%	0% -100%	

F: repeated measures ANOVA, SD: standard deviation

Table 5: Effect of multidimensional intervention on the studied thalassemic children' serum ferritin levels

Serum ferritin	Mean \pm SD	Range	F (P)
Pre intervention	4623.9 \pm 3043.1 μ g/ml	1000.0 \pm 14627.0 μ g/ml	
Post intervention	3992.1 \pm 2786.5 μ g/ml	606.0 \pm 13108.0 μ g/ml	37.9 (0.001)*
Follow-up	3536.7 \pm 2653.3 μ g/ml	400.0 \pm 12226.0 μ g/ml	

F: repeated measures ANOVA, * P < 0.05 (significant), SD: standard deviation

References:

1. Harvey RA, Ferrier DR. Globular Proteins. In: Biochemistry, 5th ed. Baltimore, Lippincott Williams and Wilkins, a Walters Kluwer business Co.; 2011, PP: 33-34.
2. Yardumian A, Telfer P, Ryan K, Darlison MW, Miller E, Constantinou G. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK, 3rd ed. 2016; Available at: <http://ukts.org/standards/Standards-2016final.pdf>. Accessed 21 July 2017.
3. Porter J, Viprakasit V. Iron Overload and Chelation. In: Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V (Eds). Guidelines for The Management Of Transfusion Dependent Thalassaemia, 3rd ed. Cyprus, Thalassaemia International Federation; 2014, P. 42, 53.
4. Rivers AE, Srivastava A. Gene Therapy of Hemoglobinopathies. In: Herzog R, Zolotukhin S (Eds). A Guide to Human Gene Therapy. Singapore, World Scientific Publishing Co.; 2010, PP: 197-199.
5. Porter JB: Pathophysiology of Iron Overload in Thalassaemia Syndromes; Thalassaemia Reports (abstract book of 12th International Conference on Thalassaemia and Hemoglobinopathies); 2011, 8.
6. Fisher SA, Brunskill SD, Doree C, Gooding S, Chowdbury O, Roberts DJ: Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia; Cochrane Database of Systematic Reviews 2013, Issue 8. [DOI: 10.1002/14651858.CD004450.pub3]
7. Fucharoen S: The Economics of Iron Chelation in Developing Countries; Thalassaemia Reports (abstract book of 12th International Conference on Thalassaemia and Hemoglobinopathies); 2011, 9-10.
8. Fortin PM, Madgwick KV, Trivella M, Hopewell S, Doree C, Estcourt LJ: Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia; Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD012349. doi: 10.1002/14651858.CD012349.
9. Meichenbaum D, Turk DC. Facilitating Treatment Adherence: A Practitioner's Guidebook. California, Plenum Press Co.; 1987, P.19.
10. Vekeman F, Sasane M, Cheng WY, Ramanakumar AV, Fortier J, Qiu Y, Duh MS, Paley C, Adams-Graves P: Adherence to iron chelation therapy and associated healthcare resource utilization and costs in Medicaid patients with sickle cell disease and thalassaemia; J Med Econ. 2016;19(3):292-303
11. Yap AF, Thirumoorthy T, Kwan YH: Medication Adherence in the Elderly; Journal of Clinical Gerontology & Geriatrics. 2015; 7 (2016): 64-67.
12. Brown MT, Bussell JK: Medication Adherence: WHO Cares?; Mayo Clin Proc. 2011; 86(4): 304-314. doi: 10.4065/mcp.2010.0575
13. Jimmy B, Jose J: Patient Medication Adherence: Measures in Daily Practice; Oman Med J. 2011; 26(3): 155-159. doi: 10.5001/omj.2011.38
14. Morisky DE, Ang A, Krousel-Wood M, Ward HJ: Predictive validity of a medication adherence measure in an outpatient setting; J Clin Hypertens (Greenwich). 2008; 10(5):348-54.
15. Oliveira-Filho AD, Barreto-Filho JA, Neves SJ, Lyra Junior DP: Association between the 8-item Morisky Medication Adherence Scale (MMAS-8) and Blood Pressure Control; Arq Bras Cardiol. 2012; 99(1): 649-58.
16. Pope E. Critical Review of Standard and New Methods of Assessing Compliance with Chelation Therapy in Thalassaemic Patients. Published master thesis, Pharmacology Department, University of Toronto. Canada. Available at: <https://tspace.library.utoronto.ca/bitstream/1807/13718/1/MQ51545.pdf>; 1995; Accessed at 26 May 2015.
17. Atreja A, Bellam N, Levy SR: Strategies to Enhance Patient Adherence: Making it Simple; MedGenMed. 2005; 7(1): 4.
18. Ho PM, Lambert-Kerzner A, Carey EP, Fahdi IE, Bryson CL, Melnyk SD, Bosworth HB, Radcliff T, Davis R, Mun H, Weaver J, Barnett C, Barón A, Del Giacco EJ: Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial; JAMA Intern Med. 2014; 174(2):186-193. doi: 10.1001/jamainternmed.2013.12944.
19. Insel KC, Einstein GO, Morrow DG, Koerner KM, Hepworth JT: Multifaceted

- Prospective Memory Intervention to Improve Medication Adherence; *J Am Geriatr Soc.* 2016; 64(3):561-8. doi: 10.1111/jgs.14032.
20. Al-Kloub MI, A Bed MA, Al Khawaldeh OA, Al Tawarah YM, Froelicher ES: Predictors of non-adherence to follow-up visits and deferasirox chelation therapy among Jordanian adolescents with Thalassemia major; *Pediatr Hematol Oncol.* 2014; 31(7):624-37. doi: 10.3109/08880018.2014.939792.
 21. Shah R, Trehan A, Das R, Marwaha RK: Serum Ferritin in Thalassemia Intermedia; *Indian J Hematol Blood Transfus.* 2014; 30(4): 281–285.
 22. Rofail D, Abetz L, Viala M, Gait C, Baladi JF, Payne K: Satisfaction and adherence in patients with iron overload receiving iron chelation therapy as assessed by a newly developed patient instrument; *Value Health.* 2009; 12(1):109-117.
 23. Pedram M, Zandian K, Keikhaie B, Akramipour R, Hashemi A, Ghahfarokhi F, Soudagar M: A Report on Chelating Therapy and Patient Compliance by Determination of Serum Ferritin Levels in 243 Thalassemia Major Patients; *Iranian Journal of Pediatric Society.* 2010; 2(2): 65-69.
 24. Rajish, Ibrahim MS, Sumje KW, Butul M, Khan MA: Route of administration of Iron Chelators – An Important Factor for patient Adherence and Acceptance in Multi Transfused Thalassemia Major Patients; *J. Basic. Appl. Sci. Res.* 2014; 4(11): 61-70.
 25. Badr M, Hesham M, Hassan T, Badawy S: Evaluation of Iron Chelation Therapy in Thalassemia Major Patients in East Delta of Egypt; *Hematologica* 2010; 95(s2): 701.
 26. El-Dakhakhny AM, Hesham MA, Mohamed SE, Mohammad FN: Quality of Life of School Age Thalassemic Children at Zagazig City; *Journal of American Science* 2011; 7(1): 186-197.
 27. Aboelela EM, El-Dakhakhny AM, Hesham MA, Bassam SE: Effect of Health Instructions on Improving Knowledge and Practices of Thalassemic Adolescents at Zagazig University Hospital; *Zagazig Nursing Journal* 2013; 9(2): 66-84.
 28. Bosworth HB. *Enhancing Medication Adherence: The Public Health Dilemma.* New York, Springer Healthcare Co.; 2012, PP: 8, 15, 27.
 29. Zivin K, Madden JM, Graves AJ, Zhang F, Soumerai SB: Cost-related medication non-adherence among beneficiaries with depression following Medicare Part D; *Am J Geriatr Psychiatry.* 2009; 17(12):1068-76. doi: 10.1097/JGP.0b013e3181b972d

