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The Effect of oral Administration of Cichorium Intybus on Reduction of Liver Enzymes in Patients with Major Thalassemia: Randomized Clinical Trial Study

Mohammad Reza Golpayegani[1], Yalda Shokoohinia[2], *Sevda Khashman[3], Nasim Jamshidi[4], Reza Tahvilian[5], Mansour Rezaei[6], Fereshteh Jalilian[5]

[1]Associate Professor of Pediatrics Hematology and Oncology, Department of Pediatrics, School of Medicine, Dr. Kermanshahi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran. [2]Ric Scalzo Botanical Research Institute, Southwest College of Naturopathic Medicine, Tempe, AZ, USA. [3]Pediatrician, Department of Pediatrics, School of Medicine, Dr. Kermanshahi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran. [4]Student Research Committee, Kermanshah University of Medical Sciences, Kermanshah, Iran. [5]Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran. [6]Professor of Biostatistics, Social Development and Health Promotion Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Abstract

Background: Beta-thalassemia is a common hematological disorder. The aim of this study was to determine the effect of oral administration of Cichorium intybus on reduction of liver enzymes in patients with major thalassemia.

Materials and Methods: This study was randomized clinical trial study that was conducted on 100 patients with age over 2 years and major thalassemia referred to Mohammad Kermanshahi Hospital of Kermanshah city (Iran) in 2019-2020. Eligible patients were randomly divided into two intervention (n=50), and control (n=50)groups.The intervention group received 0.028mg/kg/day Cichorium intybus as a medicinal supplement and control group received placebo for 3 months. All patients were evaluated and followed up for 6 months. The Liver enzymes levels (AST and ALT) were measured at four time periods (baseline, 1.5, 3 and 6 months after intervention). Ferritin was also measured at three time periods (baseline, 3, and 6 months after the intervention).The SPSS software version 24.0 was used to data analysis.

Results: The results of Repeated Measure ANOVA test showed that therewere significant statistical differencebetween the two groups of intervention and control in term of ALT and AST at different time periods, so that the means of ALT and AST after the interventionwere lower in intervention group than control group($P<0.05$). However, there wasno significant statistical differencebetween the two groups of intervention and controlin term of ferritin at different time periods ($P>0.05$).

Conclusion: Oral administration of Cichorium intybus can reduce liver enzyme levels (ALT and AST) in patients with thalassemia major. Therefore, Chicory administration in patients with major thalassemia is suggested.

Key Words: Children, Cichorium Intybus, ALT, AST, Major Thalassemia.

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Corresponding Author:

Sevda Khashman, MD, Pediatrician, Department of Pediatrics, School of Medicine, Dr.Kermanshahi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Email: dr.s.khashman@gmail.com

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1- INTRODUCTION

Beta-thalassemia is a common hematological disorder that is caused by a decrease or lack of beta-hemoglobin chain synthesis. This defect causes disruption of the hematopoiesis process, erythrocyte lysis, anemia and disorders due to iron overload in vital organs of the body (1-3). Thalassemia major is the most severe form of beta thalassemia which its symptoms appear before the child's second birthday (4). Studies show there are over 270 million carriers with abnormal haemoglobins and thalassemia in the world which 80 million are carriers of β-thalassemia. The 300,000 to 400,000 babies are born with a serious disorder of hemoglobin in the world annually, of which 25000 have beta-thalassemia major and the most of them are related to low and middle income countries (5-8). In Iran, about 3 million people are carriers of thalassemia, and 25,000 are suffering from thalassemia majorwhichabout 800 new cases are added each year (9, 10).

Given that the patients with thalassemia major are unable to produce sufficient amounts of hemoglobin, severe anemia develops in them which life-long and repeated blood transfusions are the only way to deal with this problem (11, 12). However, regular blood transfusions over the years lead to an overload of iron in the tissues.Overexpression of iron due to extravascular hemolysis, and increased iron uptake, lead to hemochromatosis. Massive splenomegaly, developmental disorders, cardiac myopathy, bone deformities, and endocrine disorders are complications of hemochromatosis. Cardiac disorders associated with both ventricular failure is the most common cause of death in thalassemia major patients (1, 13, 14). Since 1970, iron chelation therapy has been used to reduce iron overload in thalassemic patients. Deferoxamine (DFO, Desferal) is the oldest iron chelation that should be injected subcutaneously every 8–12 hours to reduce iron overload. However, deferoxamine may be associated with difference side effects such as allergic reactions, skin complications, erythema, bone pain and bone deformities, respiratory problems and growth retardation (2, 15-17). Today, the tendency to take herbal medicines has increased because of the side effects of chemical drugs. Various herbal remedies have been used for the treatment and protection of the liver in traditional medicine(18, 19). The Cichorium intybus Linn is commonly known as chicory or kasni is used for the treatment of liver diseases. The Cichorium intybus has antioxidant properties which seems to be due to the presence of numerous polyphenolic compounds in this plant (20, 21). Studies have shown that the Chicory plant contains more than 10 effective compounds, most of which are from chicory roots. One of these compounds is inulin, which makes up 40% of chicory root volume (22). The somestudies have suggested that inulin of chicory root extract is effective in enhancing expression of iron carrier genes, enzymes and ferritin in intestinal enterocytes , which ultimately lead to reduce in serum ferritin and change in liver enzyme levels (21, 23). Therefore, given that the limited studies about effect of Cichorium intybus on liver enzyme levels in patients with thalassemia major in Iran and worldwide; the aim of this study was to determine the effect of oral administration of Cichorium intybus on reduction of liver enzymes in Iranian patients with major thalassemia.

2- MATERIALS AND METHODS

2-1. Study design and population

The present study was randomized clinical trial study (RCTs) that was conducted aimed to determine the effect of oral administration of Cichorium intybus on reduction of liver enzymes in patients

with major thalassemia referred to Mohammad Kermanshahi Hospital of Kermanshah city (Iran), in 2019-2020. The patients were randomly divided into the two groups of intervention (n=50), and control (n=50). Inclusion criteria involves patient with age over 2 years and major thalassemia, serum ferritin <3000 ng/ml and informed consent from the patient or their parents. Exclusion criteria consisted of serum ferritin >3000 ng/ml, viral hepatitis, liver failure and incomplete treatment process and follow-up period. In this study, the selection of samples was based on easy (available) sampling. Considering 95% confidence and 80% power, the minimum required sample size was 263 people in each group that due to the existing limitations (number of patients, patient cooperation), the project was piloted on 100 people (50 patients in each group) (24). Also, two groups were matched differently before the study, in terms of some variables such as age, sex, body mass, and the use of different drugs.

2-2. Data Collection

The data collection tool was a checklist, including the demographic and laboratory variablessuch as sex, Aspartate aminotransferase (AST; units/liter), Alanine transaminase (ALT; units/liter) and serum ferritin (ng/mL) which was measured for both groups in four different time periods (baseline, 1.5, 3 and 6 months after intervention). The variables included in the checklist were collected and extracted from previous similar studies (25-27), and consultations with relevant specialists.

2-3. Intervention

The present study was triple blind randomized clinical trial study (RCTs). The population under study included patients with major thalassemia referred to Mohammad Kermanshahi Hospital of Kermanshah city (Iran) in 2020. After obtaining informed consent, the eligible patients were randomly divided into the two groups using a random number table (intervention group, n=50; control group, n=50). The intervention group received 0.028 mg/kg/day Cichorium intybus as a medicinal supplement was made in the Faculty of Pharmacy of Kermanshah University of Medical Sciences by the specialists of this faculty. In the present study, we were used the syrup containing 200 mg in 5 ml of Cichorium intybus for intervention group for 3 months. In contrast, the control group received placebo for 3 months (placebo was made in the Faculty of Pharmacy of Kermanshah University of Medical Sciences by the specialists of this faculty). It should be noted that all patients received their routine medications as scheduledand the Cichorium intybus or placebo extract was prescribed as a supplement. Then, patients were followed up in two groups for 6 months. Liver enzymes levels (AST and ALT) were measured at four times of baseline, 1.5, 3 and 6 months after intervention. Ferritin was also measured at threetimes of baseline, 3, and 6 months after the intervention. To prepare Cichorium intybus, chicory root was washed at least three times with ordinary water and once with distilled water in order to prevent any contamination. It is then spread on a clean cloth around the room and rotated once daily until the plant is completely dry. After one week, the dried plant is crushed by the mill. Then, 100 grams of the plant's root powder is mixed with 600 ml of distilled water. It is then placed on a heater at 80 ° C for one hour. After one hour, the mixture is smoothed and centrifuged to reduce solids. Next, the extract is transferred to a rotary apparatus to concentrate completely. The concentrated extract is formulated orally with USP syrup and formulated with a suitable flavoring and preservative. The obtained syrup is then poured into 200 ml matt glass and sealed.It is kept in the

refrigerator at 24 ° C until use by the patient (24, 25).

2-4. Ethical Considerations

Before the intervention, the aim of the study was explained to the patient or their parents, then, informed consent was obtained from them. In this study, all researchers were committed to the Helsinki Statement. The Ethics Committee of Kermanshah University of Medical Sciences approved this clinical trial study (ID-number: IR.KUMS.REC.1398.895). In addition, it was registered in Iranian Registry of Clinical Trials (IRCTID: IRCT20111001007677N6).

2-5. Statistical Analysis

For the descriptive analysis, mean (standard deviation [SD]), and frequency (%) were usedfor quantitative and qualitative variables; respectively. Then, in analytical analysis, Repeated Measure ANOVA test was used to compare the means of quantitative variables between two groups of intervention and controlat different time periods. In addition, for the qualitative variables in two group Chi-square test was employed. It should be noted that the SPSS software version 24.0 was used to data analysis and P-value <0.05 was considered as a significant level.

3- RESULTS

The number of boys and girls into intervention group were 24 (48%) vs. 26 (52%), and for control group were 27 (54%) vs. 23(46%). The mean age of patients in the intervention and control groups under study were 17.36 ±4.23 and 18.25 ± 4.98 years, respectively. Also, the mean BMI of patients in the intervention and control groups were 21.02 ±3.23 and 20.87 ± 3.67, years, respectively. The results of Chi-square test and independent-samples T-test for baseline variable showed that there are no significant statistical difference between the two groups under study in terms of gender (P>0.05) which the lack of significant statistical difference between the two under study in the term of baseline sex, age and BMI (Body Mass Index) can be a reason that randomization process has occurred correctly. Kolmogorov-Smirnov test was first used to measure normality. The results of this test showed that three variables ALT, AST and ferritin have normal distribution (P>0.05), therefore, the parametric Repeated Measure ANOVA test was used. **Table.1** shows the results of Repeated Measure ANOVA test that was used to compare the means of ALT between the two groups of intervention and control at different time periods. As can be seen, the results of this test demonstrated that there are significant statistical difference between the two groups of intervention and control at different times (P<0.05), so that the means of ALT after the intervention were lower in intervention group than control group. **Figure.1** shows the means of ALT in two groups of intervention and control at different times.

Table-1: Comparison of the Means of ALT in Two Groups of Intervention and Control at Different Time Periods.

Time Period	Group	Number	Mean	SD	P-value *
T1 : Before intervention	Intervention	50	84.32	31.54	<0.001
	Control	50	70.60	22.03	
T2 :1.5 months after intervention	Intervention	50	69.84	29.75	
	Control	50	68.20	22.54	
T3 :3 months after intervention	Intervention	50	59.94	25.60	
	Control	50	65.74	22.66	

T4 :6 months after intervention	Intervention	50	50.40	24.09
	Control	50	62.46	22.58

* Repeated Measure ANOVA Test, SD: Standard deviation.

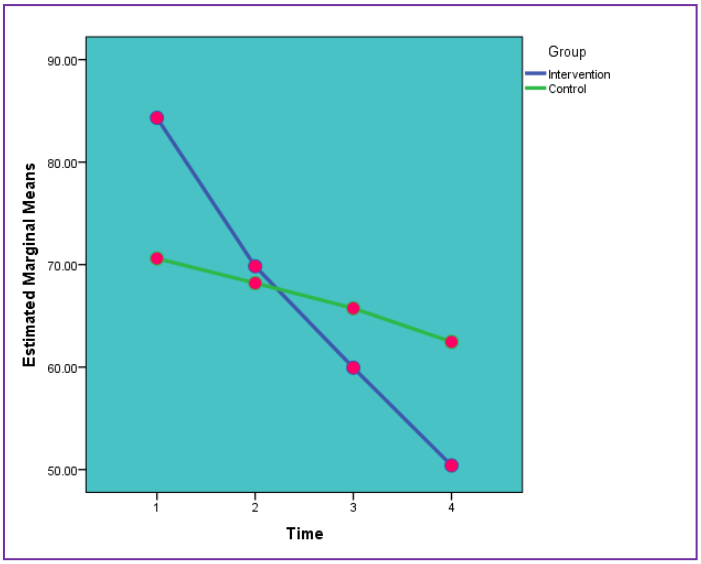

Fig 1. The Means of ALT in Intervention and Control Groups at Different Time Periods
ALT: Alanine transaminase.

Table.2 shows the results of Repeated Measure ANOVA test that was used to compare the means of ASTbetween the two groups of intervention and control at different periods. As can be seen, the results of this test demonstrated that there are significant statistical differencebetween the two groups of intervention and control at different periods (P<0.05), so that the means of AST after the intervention were lower in intervention group than control group. **Figure.2** shows the means of AST in two groups of intervention and control at different time periods.

Table-2: Comparison of the Means of AST in Two Groups of Intervention and Control at Different Time Periods.

Time Period	Group	Number	Mean	S.D	P-value *
T1 : Before intervention	Intervention	50	72.20	32.37	
	Control	50	73.26	25.20	
T2 :1.5 months after intervention	Intervention	50	61.90	29.48	
	Control	50	71.78	25.51	<0.001
T3 :3 months after intervention	Intervention	50	52.70	25.81	
	Control	50	70.72	25.21	
T4 :6 months after intervention	Intervention	50	44.18	23.58	
	Control	50	69.86	25.14	

* Repeated Measure ANOVA Test), AST: Aspartate aminotransferase,

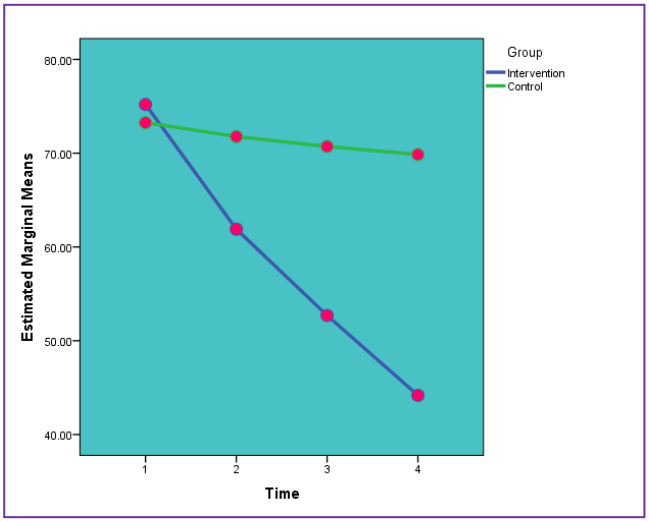

Fig.2: The Means of AST in Intervention and Control Groups at Different Time Periods
AST: Aspartate aminotransferase.

Table.3 shows the results of Repeated Measure ANOVA test that was used to compare the means of ferritinbetween the two groups of intervention and control at different time periods. As can be seen, the results of this test demonstrated that there was no significant statistical differencebetween the two groups of intervention and controlin term of ferritin at different time periods (P >0.05). **Figure.3** shows the means of ferritin in two groups of intervention and control at different time periods.

Table-3: Comparison of the Means of Ferritin in Two Groups of Intervention and Control at Different Time Periods.

Time Period	Group	Number	Mean	SD	P-value *
T1 : Before intervention	Intervention	50	1431.62	621.92	
	Control	50	1448.30	633.55	
T2 :3 months after intervention	Intervention	50	1443.10	623.62	
	Control	50	1488.24	657.94	0.287
T3 :6 months after intervention	Intervention	50	1421.00	541.78	
	Control	50	1870.54	723.95	

* Repeated Measure ANOVA Test, SD: Standard deviation.

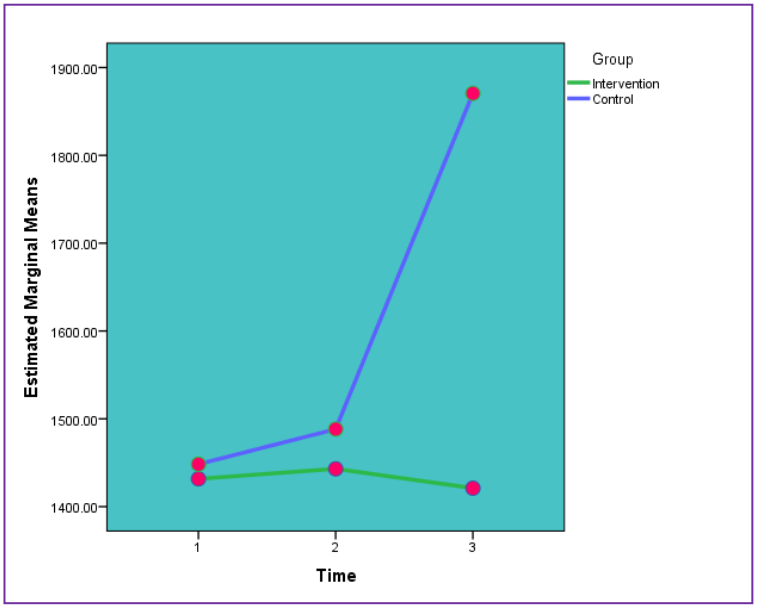

Fig 3. The Means of Ferritinin Intervention and Control Groups at Different Time Periods.

4- DISCUSSION

The aim of this study was to determine the effect of oral administration of Cichorium intybus on reduction of liver enzymes in patients with major thalassemia referred to Mohammad Kermanshahi Hospital of Kermanshah city (Iran) in 2020. The results of this study showed that there were significant statistical difference between the two groups of intervention and controlin term of ALT and AST at different time periods, so that the means of ALT and AST after the intervention were lower in intervention group than control group (P<0.05). The results are in line with previous studies. For example, in a study by Tako et al. in the United States, the results showed that inulin in some plants, such as chicory, increased the expression of ferritin-related genes, enzymes, and iron carriers in their intestinal enterocytes (26). In study by Hasani et al., aimed to determine the effect of 8 weeks of aerobic training and using Chicory extractive supplementation on serum levels of ALT and AST enzymes in women with fatty liver, the results demonstrated that the aerobic training with supplement of chicory extract had a significant effect on reducing serum levels of liver enzymes (ALT and AST), which the combination of these two interventions were more effective than either of them and there was a statistically significant difference. Finally they conclude that chicory extract has a double effect on reducing serum levels of liver cell injury markers in patients with nonalcoholic fatty liver (27). To investigate the protective effects of chicory on hepatocytes, Sadeghi et al. were investigated the effects of chicory extract on liver cell and serum levels of hepatic enzymes in rates with damagedliver,the results showed that the levels of ALT and AST enzymes decreased due to the use of this plant (28). In another study (2018), to determine the combined effect of plants extracts of jujube, artichokes and chicory on non-alcoholic fatty liver disease in rats,the results showed that the level of liver enzymes activity (ALT, AST and ALP) in serum was significantly increased with high fat diet, however, the administration of 200 mg of these extracts has been able to reduce these increased amounts (29).

Similarly, in another study conducted by Katiyar and colleagues in India (2015), on 90 newly diagnosed type 2 diabetic patients, the results showed that chicory seed extract had a better effect in reducing liver enzymes in patients with type 2 diabetes than metformin recipients. The study also suggested that treatment with chicory extract had a better effect than raw chicory powder (30). In a study by Helal et al. (2011) in Egypt on albino mice with fatty liver, the results of the study showed that chicory extract improved many biochemical parameters and histopathological changes. In addition, treatment with chicory before inducing fatty liver provides protection against fatty liver. Finally, chicory extract was recommended as a dietary supplement for fatty liver patients (31). In a similar study conducted by Shahvazian et al., in Iran (2018), aimed to assess the effect of chicory on reduction of serum ferritin and liver enzymes in patients with thalassemia major, the results showed that the mean serum levels of AST (25.44 to 22.25), and ALT (30.861 to 25.085 units/liter) decreased after chicory extract, but this decrease was not statistically significant (32). The lack of statistically significant differences may be due to the difference in the method of Chicory extract preparation and the dose used and the low number of patients studied. Finally, in our study, there was no significant statistical difference between the two groups of intervention and control in term of ferritin at different times (P>0.05). This result is consistent with the results of studies in this field (32, 33). As can be seen, the results of the present study are consistent with the above studies (26, 31). Although, these studies may differ in terms of disease type, method of operation, type of human / animal sample and the number of patients of under study, however, the results of all these studies indicate the effect of chicory extract on the reduction of liver enzymes. In addition, the results of animal studies, some of which were mentioned above (30), although the samples studied and the method employed differ from those of our study, however, administration of chicory extract as a dietary supplement was found to be beneficial for reducing liver enzymes.

4-1. Strengths and Limitations of the study

The present study has strengths and limitations. To our knowledge, this study is one of the few intervention studies, which was, investigated the effect of oral administration of chicory extract on hepatic enzymes reduction in patients with thalassemia major in Iran. The second strength of the study is the appropriate sample size and the equal number of patients in the two comparison groups, which leads to an increase in the statistical efficiency of the study. In addition, the long follow-up period of the examined outcomes is another strength of this study. Also, this study has limitations like many other studies. One of the limitations of this study is the possibility of taking medications thatmay cause interactions with chicory extract due to lack of cooperation and complete accompaniment of the patient.

5- CONCLUSION

The present study showed that oral administration of Cichorium intybus can reduce liver enzyme levels (ALT and AST) in patients with age over 2 years and thalassemia major, therefore, Chicory administration with dose of 0.028 mg/kg/day in patients with major thalassemia for 3 months is recommended.

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7- CONFLICT OF INTEREST: None.

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