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THE INVESTIGATION OF THE EFFECT OF GREEN TEA ON THE IRON OVERLOAD IN PATIENTS WITH MAJOR THALASSEMIA UNDER REGULAR BLOOD TRANSFUSION

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Abstract:

Introduction: *Major thalassemia is the most severe form of thalassemia, in which the life of patient necessarily depends on the regular infusion of blood. Blood transfusion in thalassemic patients has led to iron accumulation. The effect of green tea on the reduction of iron overload in animal samples has been confirmed. Green tea is also beneficial in the treatment and prevention of many diseases due to its antioxidant properties. The objective of this study is to determine the effect of green tea iron overload deficiency in patients with thalassemia.* ***Materials and Methods:*** *This clinical trial study was performed on 50 patients with thalassemic patients undergoing blood transfusion therapy in Zabol, Iran. The samples were randomly divided into two groups of green tea and control. At first, the demographic characteristics form was completed by patient records and the level of serum ferritin was measured before the intervention, then the patients in the intervention group received 2 grams of green tea provided by the researcher daily, three times, after each main meal for a month and after the intervention, the level of serum ferritin was measured. To measure serum ferritin, Elisa method and Tecan a-55-82 were used. Data was analyzed using SPSS software.* ***Results:*** *The mean serum ferritin in the green tea group decreased significantly after the intervention ($p < 0.05$). Also, in the control group, the mean serum ferritin level increased significantly after the intervention ($p < 0.05$) compared to before the intervention ($p < 0.05$). There was no significant difference between the mean serum ferritin in the two groups ($p = 0.109$). However, there was a significant difference between the mean serum ferritin in the two groups, after the intervention ($p < 0.05$).* ***Conclusion:*** *Our study provides valid evidence that green tea reduces serum ferritin in patients with major thalassemia. Therefore, with consideration of other beneficial effects of green tea, it is recommended that this tea with iron chelators to be used in thalassemic patients to reduce the iron overload.*

Keywords: *iron overload, green tea, thalassemia, serum ferritin*

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INTRODUCTION:

Thalassemia is a heterogeneous group of hereditary anemia due to defects in the production of one or more globin chains (1). Thalassemia considering disturbance in the alpha and beta chains is divided into two types of syndrome of alpha-thalassemia and beta-thalassemia. Beta thalassemia major is one of the beta-thalassemia syndromes that occurs as a homozygous or heterozygote due to the mutation of both beta-chain gene (3 and 4).

Iran with about 25 thousand thalassemia patients and three millions carriers is among areas where thalassemia is uncommonly common. The abundance of beta-thalassemia gene in different parts of Sistan and Baluchestan with about two million people in South-East Asia is between 4 and 10% (5).

Major thalassemia is the most severe form of thalassemia and is associated with an anemia that threatens life, so that individual life is necessarily dependent on regular blood transfusions and frequent care. Otherwise, the rate of hemoglobin decreases by less than 5 grams per deciliter (6).

Since each unit blood contains about 250-300 mg of iron, which is equivalent to two years of iron absorption from the gastrointestinal system, repeated blood transfusions in thalassemic patients lead to excessive accumulation of iron in the body (7). Among thalassemic patients, the heart and endocrine suffer the most damage, so that if the patient tolerates anemia, he/she eventually dies due to heart and glandular failure (8).

1 to 2 grams of iron per unit of blood injected into the patient is excreted daily and the rest is stored, so patients need to use iron chelators to prevent hemosiderosis and damage to various organs (9). Although *Deferoxamine* is a gold standard for treating iron chelate and has a strong demonstration of its beneficial effects in reducing ill and mortality, it is still not defined as a single therapeutic strategy (10). And according to studies, these patients are still at risk for the disease due to increased storage of body iron (12 and 11), therefore, the need for an accurate assessment of the incidence and prevention of complications is required.

One of the tools for this assessment, and one of the factors that can be used to measure the adequacy of treatment with iron chelators, is to examine the level of blood ferritin. The best indicator for determining the iron status and its overload is ferritin serum. The best level of serum ferritin to prevent the effects of iron overload in a patient with major thalassemia is 1500-1000 µg / L (13, 14 and 15). There are also methods for liver sampling, which are not preferred due to possible complications such as peritonitis (16).

As noted, thalassemic patients need to be treated with iron chelators to prevent iron overloads (16). However, despite the treatment with iron chelator drugs, including Deferoxamine, these patients are still at risk for the disease due to increasing iron stores in the body (12, 11). Therefore, lifestyle and diet in these patients is very important and the consumption of food and herbs, which their effect on the reduction of iron overload has been proved is necessary.

There is a negative correlation between tea consumption and serum ferritin level and iron overload (15). Nowadays, medicinal plants play a significant role in health and medicine in new therapeutic approaches (17 and 18).
Among the herbs used today to treat many diseases, tea can be described as one of the best and most used ones (19 and 20).

The main ingredients in herb tea include Hypericin and Hyperfluoric acid. This plant also contains caffeine, flavonoids and phenolic compounds (21). Tea is obtained from the drying of young leaves of the Camelliasinensis plant, and the difference between all types of tea is related to the operation that occurs after the leaf is picked. And they are called green, black, red and white tea (22).

Tea is the most widely used drink throughout the world (23). Iran, with a population of about 1 percent of the world's population, accounts for about 4 to 4.5 percent of total world tea consumption, and per capita consumption of tea in Iran is four times more than global per capita consumption (24).

Green tea is a type of tea that is produced by drying and steaming the new leaves of the Camilaeinensis plant, and no fermentation or oxidation action is performed on it (25, 26) and this type of tea as a therapeutic substance is a low-risk supplement to promote the public health (27). Green tea is rich in polyphenolic compounds and due to them has antioxidant properties (29 and 28). This tea as an antioxidant has anti-inflammatory, anti- -mutational and anti-cancer effects and has beneficial effects in diabetes, Parkinson's disease, Alzheimer's disease, stroke and obesity (31, 30). Due to the prophylactic properties of chronic diseases, has been particularly popular (32) and approved by the Consumer Affairs Agency as a health food. In several studies, the beneficial effects of green tea on the treatment and

prevention of many diseases have been proven (35, 34 and 33).

Green tea blocks the iron deposition in the rat liver and can be used in conjunction with iron chelators in patients with thalassemia (36, 37). Epigallocatechin gallate and Epicatechin gallate are the main components of green tea resulted in a decrease in serum ferritin (38 and 39). In a study on mice, it was found that four months of infusion of green tea extract led to a decrease in plasma iron and concentration of ferritin and TIBC (40). Mahdieh Sadat Badie in a study in 2015 found that daily consumption of 12 grams of green tea with deferoxamine leads to treatment of iron overload in patients with thalassemia (41). Green tea through two mechanisms reduces iron overload in patients with thalassemia: a) inhibits the absorption of iron other than the digestive system; b) reduces the bonded iron; and oxidative stress of red blood cells by mediation of Epigallocatechin -3- Galate and Epicatechin -3- Galate (42). In a study in 2015, tea as a repellent of iron in the diet of children with major thalassemia reduced serum ferritin (43).

Considering the high consumption of tea by the Iranian people (33) and the high probability of admission of intervention by samples and the limitation of studies done in this regard and confirmation of the effect of green tea on iron overload in animal samples (38, 39 and 40) and according to antioxidant properties and other properties that have been proven for green tea and have been effective in the treatment and prevention of many diseases (30, 31, 32, 33, and 34), therefore, the present study aimed to investigate the effect of green tea on iron overload in patients with major thalassemia in Zabol.

MATERIALS AND METHODS:

The present study is a clinical trial study aimed at determining the effect of green tea on iron overload in patients with major thalassemia in Zabol city. Sample size in this study was considered 50 subjects by using study of Sadat Badiy et al (41). Then, from among patients, the subjects who had inclusion criteria of the study were entered in the study and randomly divided into two groups of intervention (25 persons) and control (25 persons). The inclusion criteria of study were the lack of sensitivity to various kinds of tea, the lack of consumption of foods containing polyphenol, such as coffee and chocolate over the past week, the willingness to participate in the study, the non-use of other herbal remedies during the last week, the age range of 8-20 years (44) serum ferritin levels greater than 1000 micrograms per liter (14) and transfusion of blood twice a month.

One of the tools of this research was the demographic profile form, which consists of two parts: the first part includes variables such as age, gender, marital status, height and weight and occupation, and the second part examines the information related to the disease, including cases such as the duration of the disease, the number of blood transfusion in the month and the duration of blood transfusion. To measure the iron overload, the serum ferritin level was measured using ELISA (enzyme-linked immunoabsorbent assay) method and tecan a-5582. Hossein Shahdadi and colleagues have confirmed the validity and reliability of this device in their study (14). Also, to determine the amount of ferritin the ELISA method was used, for example, Saeedeh Firoozbakht and Hassan Shahdadi have also used it in their studies (7 and 14). In order to confirm the scientific validity of the device, at each test stage, the device was set up and calibrated with low, medium and high standards and all ferritin tests were carried out in one environment by one person and one device. To determine the reliability of the device and test kit, a sample was tested twice. In this study, a booklet on social hygiene diet and physical activity of thalassemic patients was provided to them.

In order to collect the data, after presenting the written form of the research unit of Zabol University of Medical Sciences to the head of Imam Khomeini Hospital in Zabol and the officials of the Special Diseases Center and performing the necessary coordination, the thalassemic section of the special patient center of Zabul was referred. After the necessary explanation to patients about the study purpose, procedure, information confidentiality and observing the diet, written consent was obtained from the patients, and then the demographic characteristics questionnaire was completed by interviewing and patients records.

For patients in both groups and their families, training was provided to patients or their families about the diet and social health and physical activities that should be followed during intervention, and a related booklet on better and more efficient education and training was provided to them. It should be noted that patients received their usual medical treatment in accordance with the past and on the basis of their physician prescriptions, without any modification or limitation.

To determine the iron overload and measure serum ferritin levels before the intervention, patients were

presented at the experimental site that were ready for the study and their blood samples were taken to determine serum ferritin levels. The intervention was then performed in patients in the intervention group so that for one month, daily and after each meal, 2 grams of green tea provided by the researcher in a quantity of water as a glass (200 ci C) for 5 minutes and then with a sugar cub (5 mg) (41, 42) and also to the control group and their families, like the intervention group, were provided training about diet and activities and social health and they received relevant educational pamphlets, and no interventions were carried out for them, and as they used to do, they continued to consume tea during the intervention.

During the study, the researcher through weekly phone calls, as well as visiting in person patients and their families made sure on compliance with the conditions of the intervention, in such a way that each patient's tea quota was delivered in the form of specific packages for a week and at the end of the week, the remaining amount was checked and the next week's quota was given.

After intervention and consumption of tea by the intervention groups for one month, the patients were again present at the site of the lab and again, samples were taken from the research units and the level of serum ferritin was measured. In addition, patients were randomly examined and patients who did not follow the diet at each stage of the work were excluded and another was replaced. Statistical analysis was performed using SPSS version 20 and P-value less than 0.05 was considered significant.

FINDINGS:

The average age of the participants was 14.34 years with a standard deviation of 3.97. The youngest and oldest participants were 8 years old and 20 years old respectively. The mean age of thalassemia was 13.89 years with a standard deviation of 3.94. In the green tea group, 12 (48%) were men and 13 (52%) were women, and in the control group, 13 (52%) were men and 12 (48%) women. The mean duration of disease in the green tea group was 14.82 years and in the control group it was 12.72 years. The mean transfusion time in the green tea and control group was 13.67 and 10.70 years, respectively.

In table 1, mean serum ferritin was compared in both groups before and after the intervention. The results showed that there was no significant difference between serum ferritin before and after intervention ($p = 0.065$).

Table 1: Comparison of serum ferritin levels in the two groups before intervention

Group	Before intervention	Statistical test	p-value
	Mean (SD)		
Green Tea	3889.23(1558)	Kruskal Wallis	0.065
Control	2958.62(1373.10)		

Also, mean serum ferritin was compared in two groups after the intervention using Kruskal Wallis test. Results showed significant differences between two groups after intervention in serum ferritin level ($p < 0.007$) (Table 2).

Table 2: Comparison of serum ferritin levels in two groups after intervention

Group	After intervention	Statistical test	p-value
	Mean (SD)		
Green Tea	2222.50 (1539)	Kruskal Wallis	0.007
Control	3418.84(1247.40)		

Table 3: Comparison of serum ferritin before and after intervention in each group

Group	Before intervention	After intervention	Statistical test	p-value
	Mean (SD)	Mean (SD)		
Green Tea	3889.23(1558)	2222.50 (1539)	Paired t	<0.001
Control	2958.62(1373.10)	3418.84(1247.40)		

In table 3, using t-test, mean serum ferritin in each group was compared before the intervention. The results showed that mean serum ferritin in the control group reached from 2958.62 ng / dl before intervention, to 3418.84 ng / dl, which was statistically significant ($p < 0.001$). In the intervention group, after taking green tea, the mean serum ferritin reached 3889.23 to 2222.50 ng /dL, which was statistically significant ($p<0.001$). The results showed that green tea had a significant effect on serum ferritin levels, and the serum ferritin and iron overload was also significantly increased in the control group.

DISCUSSION AND CONCLUSION:

The results of this study showed that the mean serum ferritin reduction in green tea users was significantly higher than that in the control group. Green tea had a significant effect on reducing the iron levels of thalassemic patients.

There is a negative relationship between tea intake with serum ferritin and iron overload, and as tea consumption increases, serum ferritin levels are reduced (15). Tea is known to be a potent inhibitor of iron intestinal absorption. One of the strongest ligands for inhibiting iron intestinal absorption is tannins (45). Green tea is rich in tannin (tannic acid) (46). Therefore, tannin plays a major role in reducing the iron levels of patients.

The results of experiments in physiological conditions have shown that tea polyphenols with iron form an insoluble complex. This transplantation in the stomach causes iron not to be absorbed. The effect of phenolic compounds on iron absorption has been investigated and it has been shown that phenolic compounds, including phenolic monomers, polyphenols and tannins, by forming complexes with iron, reduce the availability of iron to be absorbed in the body. Then, the properties of phenolic compounds for iron binding were investigated, and it was found that polyphenols act partly as an antioxidant by forming a complex of iron 2 (47). The researchers have found that the polyphenols contained in tea bind to iron in the intestinal cells and create a non-transferable compound that can't enter the bloodstream, and therefore it is excreted through feces (48).

Green tea is rich in polyphenolic compounds, so that the amount of these compounds in green tea is about twice that of black tea (46 and 49). Green tea, therefore, can be very useful in reducing the iron overload due to its phenols. In addition, the polyphenolic compounds in green tea have created a lot of antioxidant properties for this substance, which, as an antioxidant, can prevent the oxidation and degradation of red blood cells (36 and 37). Considering that one of reason of iron overload in thalassemic patients is the destruction of red blood cells and the release of iron into the bloodstream (50), therefore, green tea with its antioxidant effect is likely to be effective in reducing the iron overload in these patients.

Iron excretion, when it is low in the body, is caused by feces, but with iron overload and increased iron levels in thalassemic patients, iron excretion is through renal excretion and urinary excretion (50), another issue could possibly explain the chelate effect of tea, is diuretic effect, which is due to caffeine contained in tea, that caffeine leads to renal vascular dilatation and increases the blood flow of the kidneys and, consequently, increases the excretion (51) through which leads to more iron excretion.

Green tea can also inhibit iron absorption from the digestive tract and reduce the oxidation of red blood cells due to its catechin, such as epigallocatechin gallate -3-galate and epicatechin -3-galate. (42) Epigallocatechin gallate through reaction with iron creates an EGCG-Fe compound and prevents the iron reaction, thereby reducing iron overload, and Guan-Hu Bao concluded this in their study in 2013 (52). Various studies have also confirmed that green tea is used as a natural iron chelator due to the presence of epigallocatechin gallate and epicatechin gallate, and can be combined with iron chelators in patients with major thalassemia under repeated blood transfusions to reduce serum ferritin levels in patients (36, 36 and 40).

Elmoneim et al., in a study conducted in Saudi Arabia in 2015, found that a diet containing iron repellents, which includes tea consumption in this diet, could reduce serum ferritin levels from 3538.5 µg / lit to 2456.5 µg in liter in patients with major thalassemia (43). The results of this study indicate that tea with an iron repellent diet and low iron diet may have an effect on the overload iron in patients with major thalassemia, which is consistent with the results of the present study.

In a study by Saewong in Thailand in 2010 on rats, the study concluded that taking green tea extract of 300 mg / body weight plus 50 mg / day of oral Deferiprone for 8 weeks resulted in reducing iron deposition in the liver of rats and reducing the amount of iron in the rats (37). Mahdieh Sadat Badiey and colleagues in a study conducted in Torbat-Heydarieh concluded that consuming 12 grams of green tea per day for one month with *Deferoxamine* can lead to a significant decrease in serum ferritin and iron overload in thalassemic patients (41). The results of these two studies indicate that taking green tea with iron chelator can lead to a reduction in the iron overload in patients with major thalassemia. Green tea improves the effects of iron

chelators on excretion and prevents iron absorption in the small intestine, and is thus recognized as a very suitable supplement for chelators to reduce iron overload (53). Therefore, the studies of Si Wong and Sadat Badyei are consistent with the results of this study.

Another study by Ounjaijean in 2008 found that the administration of four months of green tea extract in rats could lead to a decrease in plasma iron and serum ferritin concentrations in rats (40). In a 2014, Jetsrisuparb concluded in a case report that after 11 months of daily consumption of two cups of green tea can reduce serum ferritin levels from 1090 micrograms per liter to 600 micrograms per liter (42). Lee and Thephinlap, in separate studies of the effects of green tea on the reduction of iron overload and the level of serum ferritin in patients with iron overload, suggesting that the active compounds present in the green tea act as natural iron chelator (38 and 39), the results of which are consistent with our study results.

In 2001, Samir Samman et al in their study found that catechins, which are the main ingredients in green tea, making insoluble compounds in the lumen of the gastrointestinal tract prevent iron absorption and reduce the iron's viability (54). The results of the study by Samen, also expressed in one of the mechanisms of green tea in reducing the iron overload through the catechins in it, are consistent with the results of our study.

Iron overload in thalassemic patients, through the Haber-Weiss reaction, leads to oxidative reactions. In addition, iron acts as a catalyst for the conversion of hydrogen peroxide to free radicals, and also iron through the reaction of Fenton leads to damage to the membrane of the cells and damage the various cells, such as hepatocytes and mitochondria, in the heart cells (41).

Bogdanski et al showed that ECG and EGCG decrease the reactivity of free radicals by electron displacement (55). Orino, in his study, concluded that increased serum ferritin levels could be a defense mechanism against Oxidative stress and damage caused by it that green tea reducing these oxidative reactions, can lead to a decrease in serum ferritin levels and therefore an overload of iron (56), the results of which confirm the results of present study. It has also been confirmed in several studies that oxidative reactions are associated with inflammatory pathways in patients with thalassemia. Green tea reduces inflammation by reducing these oxygenates and, by antioxidant and anti-inflammatory activity, leads to improved immune function (57).

Considering the various mechanisms that the green tea helps reduce the serum levels of ferritin and iron overload, and in various studies, green tea and its compounds are referred to as natural iron chelators, which also improve the function of the chelators (36, 36 and 40), and except for the effect of green tea in reducing the iron overload, have shown many other effects in the treatment and prevention of many diseases for this tea, and this tea is a potent antioxidant (35, 34 and 33), therefore, in patients with major thalassemia under regular blood transfusion, green tea alongside chelators can be used to iron excretion and reduce its overload, and it is recommended that more studies be conducted on more people in this field.

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