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Effect of pentoxifylline on correction of anaemia due to chronic diseases in systemic lupus erythematosus

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ABSTRACT

This study aimed to evaluate the effect of Pentoxifylline on correction of anaemia of chronic diseases in systemic lupus erythematosus. Seventy patients with systemic lupus erythematosus (SLE) and anaemia aged 28.9 ± 5.6 were studied in 2013 in a clinical trial. Sampling method was random permutation blocks in two groups of control and intervention patients. Intervention group received pentoxifylline; after 4 months, haemoglobin, iron and TNFα profiles of the two groups were compared. Data were analysed using T-test. The results showed that the haemoglobin increased by 0.2mg/dl in the intervention group and 0.26mg/dl in the control group, which was statistically insignificant. Changes in ferritin, serum iron and serum iron/TIBC were respectively -3.6±58.4 µg/dl, 1.6±28.8 µg/dl and 0.02±1.0 µg/dl in the Pentoxifylline group and 2.0±59.1 µg/dl, 0.6±28.5 µg/dl and 0.01±0.1 µg/dl in the placebo group. TNFα changes were -1.5±8.8pg/dl in the Pentoxifylline group and 0.2±4.0pg/dl in the placebo group, which was not statistically significant. Therefore, receiving Pentoxifylline in anaemic patients with SLE have no effect on haemoglobin levels and iron profiles of these patients.

Keywords: Pentoxifylline, anemia of chronic disease, systemic lupus erythematosus, iron profile

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INTRODUCTION

Anaemia is a common blood disease by 18% reported prevalence in industrialized countries and 56% in developing countries, on average [1]. It refers to reduction of haemoglobin concentration to lower than in healthy subjects according to age and sex. According to the studies, about 30% of people around the world are suffering from anaemia [2]. This disease is a common finding in patients with SLE, so that the majority of patients suffering from SLE experience anaemia. Anaemia is usually mild to moderate, but occasionally it is quite severe. Anaemia in Lupus may or may not depend on immune system. Anaemia of chronic diseases often occurs in patients with infectious, inflammatory or neoplastic diseases, lasting for more than 1 or 2 months and characterized by hypothermia in presence of adequate reticuloendothelial iron reservoirs. The cause of this anaemia is multi-factorial and includes mild decrease in red blood cell lifespan, direct source of hematopoiesis, relative erythropoietin

deficiency and a reduced intake and transport of iron. SLE is an autoimmune disease detected by the presence of autoantibodies to nuclear antigens. This is a multi-system disease, and patients can have many different symptoms. In a number of patients with SLE, it can cause nephritis, neurological, psychological problems and thrombocytopenia. Over 90% of people with SLE have positive anti-nuclear antibodies (ANA) [3]. Due to the extensive efforts, pathogenesis mechanism of SLE is still not known quite accurately [4]. Constitutional symptoms such as fatigue, weight loss and fever are not life threatening symptoms, but they have a significant effect on quality of life. SLE patients often complain of poor sleep and severe fatigue [5].

Approximately 30% of SLE patients experience kidney disease; therefore, regular urinary analysis and monitoring of blood pressure is important. renal Involvement by excretion of urinary protein (<0.5g/24h) and presence of red blood cell casts is detected in urine and patients should be referred early to renal biopsy which is very important in determining prognosis [6].

More than 95% of patients with SLE have positive ANA. All patients must be examined for extractable nuclear antibodies [ENA]. Various ENAs are related to various protests of diseases. For instance, Anti-ds DNA are associated with renal involvement and anti-ro is related to secondary Sjogren's syndrome. SLE is a relapsing and extinguishing disease. Management of relapse, reducing the risk of recurrence of the disease and its relative stability, control of threatening causes are steps of treatment of this disease. Nevertheless, disabilities often become more apparent every day. Now, the primary treatment of this disease is the active use of immunosuppressant, therefore, there is a high risk of developing other infections [7]. Unlike anaemia, blood loss followed by recovery from erythropoisis returns to normal [8]. Pentoxifylline is an independent Xanthine derivative, chemically called as 1-[5-oxohexyl]-3, 7-Dimethylxanthine which inhibits Xanthine oxidase effects and Phosphodiesterase [9].

This medicine is a vasodilator, but its main activity is to reduce blood viscosity, possibly through an effect on the ability to reshape RBCs and reduce the amount of aggregation and adhesion of platelets. This medicine increases circulation to ischemic tissues and improves oxygenation of tissues in patients with peripheral vascular disease. The drug also increases oxygen tension in the cerebral cortex and cerebrospinal fluid. The drug is readily absorbed from the gastrointestinal tract with first-pass metabolism effect in the liver. Some drug metabolites are active. Half-life of the drug is 4-8 hours and unabsorbed drug often excretes within 24 hours, primarily as metabolites in the urine [10]. Due to a variety of biochemical and antioxidant properties, PTX is capable of improving capillary blood flow and tissue oxygenation [9]. In experimental models, Pentoxifylline inhibits TNF-alpha production by monocytes as well as IFN-γ production by T cells [11-12]. Numerous studies have demonstrated the role of Pentoxifylline in reducing these cytokines, particularly TNF_{α} [13-14].

Mortazavi et al (2012) studied the Effect of Pentoxifylline on haemoglobin levels and erythropoietin administered in anaemic patients receiving peritoneal dialysis. In this study, patients were randomly divided into a group of 25 patients receiving pentoxifylline and control group. Blood haemoglobin, albumin, iron, TIBC, ferritin and PTH levels were measured at the beginning and end of the study. The results of this study showed no significant differences in haemoglobin and serum albumin levels in the two groups. As a result, based on this study, receiving Pentoxifylline in anaemic patients on peritoneal dialysis had no effect on haemoglobin levels and EPO dose [15].

In another study, using vitro Pentoxifylline on isolated myocardial cells in rats with cardiomyopathy, Galindo-Rodríguez et al in Mexico (2003) could reduce TNF_{α} levels in these cells by reducing mRNA production of TNF_{α} gene input [16]. However, several studies have been conducted on the effect of Pentoxifylline in the treatment of anaemia of chronic kidney disease (17). Effect of pentoxifylline on the correction of anaemia in chronic kidney disease has been confirmed by these studies; on the other hand, Pentoxifylline, which is derived from xanthine and used as a vasodilator to treat vascular disorders for years, is oral and easily absorbed from the gastrointestinal tract without dangerous and long-term side effects. Examining the correction of anaemia of chronic patients with SLE is acceptable after administration of a 4-month treatment period with 400mg Pentoxifylline daily. Studies have shown that Pentoxifylline inhibits production of TNF alpha by monocytes as well as IFN-gamma production by T cells, and this is done by inhibiting TNF_{α} gene transcription to reduce immune inflammation [18].

However, some studies suggest that pentoxifylline is effective in increasing haemoglobin of CRF patients. Ferrari and colleagues (2010) in Australia studied 14 patients with CKD stages 4 and 5. A significant increase was found in blood haemoglobin levels of patients receiving pentoxifylline than in patients with chronic kidney disease. This study showed that pentoxifylline decreases circulation interleukin-6, and increases haemoglobin. These changes

occur by changes in saturated Transferrin circulation and ferritin associated with increased free iron. *The results of this study revealed increase in haemoglobin levels after taking Pentoxifylline in patients (19).*

Johnson et al. (2008) in Australia conducted a study on a total of 110 patients with chronic kidney disease and anaemia with haemoglobin less than 11 milligrams per decilitre who were compared in two groups, one receiving pentoxifylline and the other control group. The results of this study showed a significant increase in haemoglobin levels in patients receiving Pentoxifylline after 4 months. In addition, the rate of blood transfusion was significantly lower in these patients than in controls (20). Nazemian et al. (2007) studied patients with chronic kidney disease; the results indicated a significant increase in haemoglobin levels in patients taking Pentoxifylline (21).

In this study, the effect of Pentoxifylline on the correction of anaemia of chronic diseases in systemic lupus erythematosus has been examined. For this purpose, the mean haemoglobin in SLE patients with anaemia of chronic diseases was measured before and after receiving pentoxifylline. This has been performed before and after receiving placebo. Then, the average iron profile of patients was measured and compared before and after receiving pentoxifylline and placebo. Finally, this measurement and comparison were done on average TNF_{α} of patients.

MATERIALS AND METHODS

This research is randomized controlled clinical trial. The trail was designed as parallel. Participants included patients diagnosed with systemic lupus erythematosus in a stable phase of the disease and anemia of chronic disease. They were referred to the rheumatology clinic to detect if they suffer from anaemia or not. The results rejected the presence of anaemia in the patients for other reasons.

Inclusion criteria were:
1. Stable phase of disease in patients diagnosed with systemic lupus erythematosus
2. Lupus patients with chronic anaemia

Exclusion criteria were:
1. Patients with iron deficiency anaemia and other types of anaemia
2. SLE patients with major organ involvement
3. No history of CNS and ocular bleeding and clotting problems
4. No co-infection
5. Allergies, Hives and angioedema

Sample Size and Sampling

In this randomized controlled clinical trial, the trail was designed as parallel.
Permuted-Block Randomization was used for random allocation of patients into two groups so that the block size was two. At the same time, the two groups were adjusted according to sex, and age. The investigated disease was not prevalent; according to statistics books, there were 25 samples in each intervention and control groups. Patients were blind. There was no random selection among eligible patients. All eligible patients were selected using convenience sampling.

Table 1: variables of measurement

characteristics variables	Role of variable			Type of variable				Practical definition of the variable	Variable scale
				Quantitative		Qualitative			
	Contextual	**Independent**	**Dependent**	**Continuous**	**Discrete**	**Nominal**	**Ranking**		
Hg			*	*				Based on the experimental results	$^{mg}/_{dl}$
Ferritin			*	*				Based on the experimental results	$^{\mu g}/_{dl}$
Serum Iron			*	*				Based on the experimental results	$^{\mu g}/_{dl}$
SI/TIBC			*	*				Based on the experimental results	Saturation (%)
TNFα			*	*				Based on the experimental results	$^{pg}/_{dl}$
Administration of Pentoxifylline		*				*		400 mg	Yes-no

Stable-phase SLE patients were randomly divided into two groups relatively similar in terms of age and gender. There was no difference between patients in terms of activity. According to The randomized block permutation, patients were put in two intervention and control groups. Table 1 presents variables existing in the measurement.

A AB AB BA BA BAA BB AA BB A BBA BA ABAB : control
B BABAABAB : intervention

Materials

Laboratory tests to measure haemoglobin, ferritin, serum iron, TIBC, RPI, indirect and direct Coombs and LDH that were measured at the beginning, middle and the end of the study. TNF_{α} measurements were performed at baseline and the end of study.

Method

First, patients with systemic lupus erythematosus in the stable phase referred to rheumatology clinic and were taken blood samples for CBC; then, based on reported haemoglobin, patients with anaemia were identified. Afterwards, iron profiles of patients were determined by relevant laboratory tests to specify patients with iron deficiency anaemia to be excluded from the study, which included patients who had ferritin levels less than 40mg/dl or SI less than 18%. In addition, all patients were tested at 8 to 10 am in the fasting state to remove clock cycles on serum iron. In addition, tests of haemolytic anaemia, including RPI, LDH, direct and indirect coombs were performed on each patient. Patients with diagnosed Anaemia of chronic disease were enrolled and randomly divided into two groups. A group received 400mg daily Pentoxifylline and the other group was given placebo. Medications were in the form of capsules; in capsules of the intervention group, there was pentoxifylline and starch for the other group. At the end of the fourth month, iron profiles and tests related to haemolytic anaemia were checked. At the beginning and end of the study, TNF_{α} was checked in patients in both groups; ultimately, the results were compared within and between groups.

Data Analysis

For data analysis we used SPSS software Ver.16. Descriptive statistics, including distribution, percentage, mean and standard deviation were used to describe the data. T-Test test was used to compare quantitative variables between the two groups. All patients were on their original drug regimen and they did not deprived from their own treatment.

RESULTS AND DISCUSSION

Figure 1 shows distribution of age. Obviously, the average age of 70 patients was 28.9 ± 5.6.

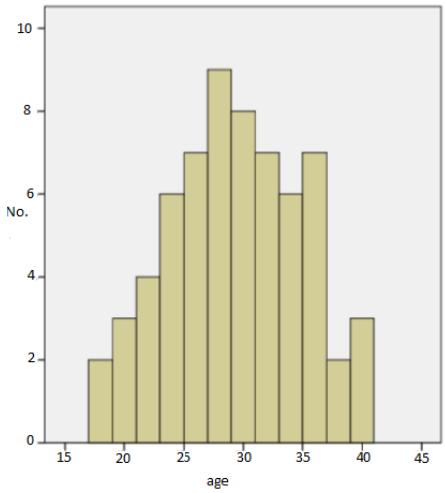

Figure 1: distribution of age

Determination of mean Hb in systemic lupus erythematosus patients with anaemia of chronic diseases after receiving pentoxifylline is an important factor in the investigations. Table 2 shows Comparison of mean haemoglobin levels in systemic lupus erythematosus patients with anaemia of chronic diseases after receiving

Pentoxifylline using paired t-test. Clearly, the mean haemoglobin level was 11.4±1.5mg/dl before intervention and 11.6±1.2mg/dl after receiving Pentoxifylline. This difference was not statistically significant in the group receiving Pentoxifylline (P= 0.221).

Table 2: comparison of mean haemoglobin in SLE patients with anaemia of chronic diseases after receiving pentoxifylline using paired t-test

	Before intervention mg/dl	After intervention mg/dl	p-value
Hemoglobin levels	11.4±1.5	11.6±1.2	0.221

Mean Hb was determined in SLE patients with anaemia of chronic diseases after receiving placebo. Table 3 indicates the comparison of mean haemoglobin levels in SLE patients with anaemia of chronic diseases after receiving placebo using paired t-test. As the table shows, mean haemoglobin of the control group was 11.3±0.7mg/dl before the intervention, as 11.5±0.9mg/dl after receiving placebo. This difference was also statistically insignificant (P=0.101).

Table 3: comparison of mean haemoglobin in SLE patients with anaemia of chronic diseases after receiving placebo using paired t-test

	Before intervention mg/dl	After intervention mg/dl	p-value
Hemoglobin levels	11.3±0.7	11.5±0.9	0.101

The mean haemoglobin level was compared in patients with SLE patients with anaemia of chronic diseases after receiving Pentoxifylline and placebo using independent t-test, as shown in Table 4. Clearly, haemoglobin level changed by 0.2mg/dl in intervention group and 0.26mg/dl in control groups, which was not statistically significant (P=0.745).

Table 4: Comparison of Hb before and after the intervention in both groups receiving pentoxifylline and placebo using the independent t-test

	Pentoxifylline	Placebo	p-value
Hemoglobin before the study	11.4±1.5	11.3±0.7	0.622
The amount of changes of hemoglobin	0.2±0.9	0.26±0.8	0.745

As noted above, an important factor in these investigations is to determine the average profile of iron.
Table 5 shows the comparison of iron profile (including serum ferritin, serum iron and ratio of serum iron to TIBC) before and after receiving pentoxifylline using paired t-test. As data shows, ferritin was 131±65.4µg/dl before intervention and 127.4±51.5µg/dl after intervention; levels of serum iron were 82.5±27.4µg/dl before intervention and 84.1±30.2µg/dl after intervention. The ratio of serum iron to TIBC was 0.19±0.08 before and 0.21±0.09 after intervention. No significant difference was found before and after treatment (P>0.05).

Table 5: Comparison of iron profile (including ferritin, serum iron and the ratio of serum iron to TIBC) before and after receiving pentoxifylline using paired t-test

Iron profile	Before	After	p-value
Ferritin	131±65.4	127.4±51.5	0.132
Serum iron	82.5±27.4	84.1±30.2	0.108
The ratio of serum iron to TIBC	0.19±0.08	0.21±0.09	0.475

Mean iron profile was determined in SLE patients with anaemia of chronic diseases before and after receiving placebo using the data available in Table 6. The data suggest that ferritin was 120.3±57.4µg/dl before and 122.3±60.9µg/dl after intervention; levels of serum iron were 80.6±27.2µg/dl before and 81.2±29.8µg/dl after intervention. The ratio of serum iron to TIBC was 0.23±0.1 before and 0.24±0.11 after intervention. No significant difference was found before and after treatment (P>0.05).

Table 6: Comparison of iron profile (including ferritin, serum iron and the ratio of serum iron to TIBC) before and after receiving placebo using paired t-test

Iron profile	Before	After	p-value
Ferritin	120.3±57.4	122.3±60.9	0.341
Serum iron	80.6±27.2	81.2±29.8	0.411
The ratio of serum iron to TIBC	0.02±0.09	0.24±0.11	0.281

Table 7 shows Comparison of changes in average iron profile before and 4 months after the intervention in groups receiving pentoxifylline and placebo using independent t-test. The results show that the rate of changes in ferritin, serum iron and ratio of serum iron to TIBC was -3.6±58.4µg/dl, 1.6±28.8µg/dl and 0.02±0.1, respectively, in the pentoxifylline group and 2.0±59.1µg/dl, 0.6±28.5µg/dl 0.01±0.1, respectively, in the placebo group. There was no significant difference between those groups (P>0.05).

Table 7: comparison of changes in iron profile before and after 4 months of intervention in groups receiving pentoxifylline and placebo using independent t-test

Iron profiles	Pentoxifylline	Placebo	p-value
Ferritin	-3.6±58.4	2.0±59.1	0.569
serum iron	1.6±28.8	0.6±28.5	0.211
ratio of serum iron to TIBC	0.02±0.1	0.01±0.1	0.854

Results of determining the average changes in TNF_α in SLE patients with anaemia of chronic disease before and after receiving pentoxifylline are shown in Table 8. This table shows the amount of TNF_α was 11.7±7.9pg/dl before the intervention and 10.2±10.6pg/dl after receiving pentoxifylline, which was not statistically significant (P=0.342).

Table 8: comparison of mean TNF_α before and after receiving pentoxifylline using paired t-test

	Before	After	p-value
TNF_α	11.7±7.9	10.2±10.6	0.342

The average TNF_α was determined in SLE patients with anaemia of chronic disease before and after receiving placebo, as shown in Table 9. The amount of TNF_α was 11.7±9.1pg/dl before the intervention and 11.9±9.2pg/dl after receiving placebo, which was not statistically significant (P=0.769).

Table 9: comparison of mean TNF_α before and after receiving placebo using paired t-test

	Before	After	p-value
TNF_α	11.7±9.1	11.9±9.2	0.769

Table 10 compares the average changes in TNF_α in SLE patients with anaemia of chronic disease after receiving pentoxifylline and patients receiving placebo. TNF_α changed by -1.5±8.8pg/dl in the pentoxifylline group and 0.2±4.0pg/dl in the placebo group; the difference was not statistically; significant (P=0.343).

Table 10: comparison of changes in TNFα before and after the intervention between two groups receiving pentoxifylline and placebo using independent t-test

	Pentoxifylline	Placebo	p-value
TNFα prior to the study	11.7±7.9	11.7±9.1	0.999
TNFα changes	-1.5±8.8	0.2±4.0	0.343

So far, no study has been done on the effect of Pentoxifylline on anaemia in systemic lupus erythematosus, but several studies on the effects of pentoxifylline in the treatment of anaemia of chronic kidney disease have been done. Mortazavi et al (2012) studied the effect of Pentoxifylline on haemoglobin levels and the amount of erythropoietin on anemic patients undergoing peritoneal dialysis. In this study, the patients were randomly divided into two groups of 25 subjects receiving Pentoxifylline and the control groups. The amount of hemoglobin, albumin, iron, TIBC, ferritin, and parathyroid hormone (PTH) levels were measured at the beginning and the end of the study. The results showed no significant differences in changes in hemoglobin and serum albumin levels in the two groups. On the other hand, receiving Pentoxifylline on peritoneal dialysis in anemic patients did not have a significant effect on the levels of hemoglobin and erythropoietin dose.

However, some studies suggest that Pentoxifylline is effective in increasing hemoglobin CRF patients. In Ferrari's (2010) Australian study, 14 patients with CKD stages 4 and 5 were studied. In patients receiving Pentoxifylline, significantly increased hemoglobin levels compared to patients with chronic kidney disease. This study showed that Pentoxifylline decreases interleukin-6 in the circulation and increases hemoglobin.

Also, in cooper et al study (2004) 16 ESRD patients were studied in a 6-month cohort study in England. Renal failure patients with erythropoietin resistant anaemia received 4 months Pentoxifylline. The hemoglobin level rose from 9.5 to 11.7 and the TNFa levels dropped from 58% to 31%.

We can say that because of the nature of the systemic lupus erythematosus disease or other relevant factors, Pentoxifylline failed to increase hemoglobin level and modify anaemia in patients with SLE although this effect in most of the studies on the renal disease has been observed.

CONCLUSION

In this study, Pentoxifylline could reduce the amount of TNF-alpha. However, haemoglobin in patients treated with pentoxifylline did not differ from control groups. Systemic lupus erythematosus is a chronic inflammatory disease in which the presence of various cytokines has been suggested. It is likely that these cytokines intense anaemia in patients and Pentoxifylline cannot inhibit it and hence the haemoglobin was not increased after treatment. In conclusion, Pentoxifylline failed to increase haemoglobin in SLE patients and correct their anaemia due to the nature of systemic lupus erythematosus or other relevant factors. Although most studies conducted on renal patients observed this effect. The findings suggest that receiving Pentoxifylline in anaemic patients with SLE has no effect on haemoglobin levels and iron profiles.

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