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Research Article

Effects of Pentoxifylline on Inflammatory Factors and Quality of Life in Maintenance Hemodialysis Patients

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Abstract

Background: Increased inflammatory cytokines including C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) are a common finding in patients with particularly those with end-stage renal disease (ESRD), which can lead to several complications in these patients and reduce their quality of life. Considering the anti-inflammatory effects of pentoxifylline, this drug could play a role in reducing inflammatory factors and improving quality of life (QoL) of hemodialysis (HD) patients.

Methods: In this randomized placebo-controlled trial 88 chronic HD patients were divided into two groups with equal numbers. The intervention group received a tablet of pentoxifylline 400 milligrams and control group received the matching placebo, daily for 3 months. At baseline and after 3 months, inflammatory factors including serum levels of TNF-α and CRP were measured. Also, the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) QoL questionnaire was completed by each patient at the beginning and end of the study.

Results: Significant reduction in serum levels of TNF-α, and CRP as well as substantial improvement of all dimensions of QoL were observed in the intervention group after 3 months of pentoxifylline treatment ($P = 0.04$; $P < 0.001$, $P < 0.05$ respectively). Between groups comparison showed a marked reduction in inflammatory markers including TNF-α and CRP in recipients of pentoxifylline than the control group at the end of the study ($P = 0.003$ for both). In addition to dimensions of physical component score (PCS), mental component score (MCS) and overall score of QoL showed significant improvement in the pentoxifylline group compared to the placebo group at month 3 of the study ($P = 0.003$; $P = 0.027$, $P = 0.002$ respectively).

Conclusion: Use of pentoxifylline in HD patients illustrated positive effects on inflammation and health-related QoL.

Introduction

In chronic kidney disease (CKD) patients, particularly those with end-stage renal disease (ESRD), the equilibration of most biochemical factors such as cytokines is widely dysregulated, causing many complications like persistent inflammation.[1-3] As a result of the loss of this balance, ESRD patients suffer from many complications, which are common and can even cause persistent infections.[3]Many inflammatory mediators are involved in the systemic inflammation of hemodialysis (HD) patients, including CRP, IL-6, TNF-α, IL-1, and IL-2. TNF-α and CRP are considered more important. TNF-α is one of the cell signaling proteins that play a role in systemic infections and is one of the cytokines that cause acute phase reactions of inflammation. This factor is mainly produced by macrophages and also by CD4+, NK cells, neutrophils, mast cells, eosinophils, and neurons.[3] Following the release of IL-6 from macrophages and T cells, it increases. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells to activate the complement system. In clinical applications, it is known as the most common biomarker for measuring inflammation.[3] On the other hand, patients undergoing (HD) are at high risk of chronic inflammatory state due to the conditions such as increased generation of pro-inflammatory cytokines, excess generation of endotoxins, oxidative stress and decreased levels of antioxidants, comorbidities and some complications of dialysis

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including chronic vascular access, intravenous catheter, biofilm formation, latent or recurrent infection or clotting of arteriovenous access.[3-5]

The dialysis process and persistent inflammation, together lead to major complications including anemia, malnutrition, infection, depression, musculoskeletal disorders, and atherosclerosis cardiovascular disease, which are known as the most important mortality predictors among HD patients.[6-8]

In addition, there are many studies demonstrating that CKD patients have a lower quality of life (QoL) than healthy people.[9] Patients with ESRD have more physical pain, less vitality, more physical, mental, and social dysfunction, and a more limited ability to manage their daily lives than healthy people. Physical symptoms such as fatigue, lack of energy, body pains, and limitations in social life are among the most important factors deteriorating these patients' QoL.[10-12]

Pentoxifylline is one of the medications used frequently by dialysis patients. It is a xanthine derivative, and non-selective competitive inhibitor of phosphodiesterase that the increases intracellular concentration of cyclic adenosine monophosphate (cAMP). This medication inhibits TNF-α and leukotriene synthesis, improves erythrocyte deformability and decreases the viscosity of blood, platelet aggregation, and clotting formation. As a result, ischemia caused by low blood supply to the muscles is reduced, and fewer spasms and intermittent claudication are achieved. It is also an adenosine 2 receptor antagonist.[13] The general objectives of this study were to investigate the effect of pentoxifylline on the serum levels of TNF-α and CRP, as well as on QoL of HD patients.

Methods

Study population

This was a single-blind, placebo-controlled, randomized clinical trial that was approved by the judicial ethics committee of Tabriz University of Medical Sciences with the ethics code number IR.TBZMED.REC.1397.954. The study was conducted at three hospitals (Imam Reza, Sina, and 29 Bahman) on chronic HD patients who were not involved in other investigations or clinical studies. Finally, after the implementation of inclusion and exclusion criteria, a total of 88 HD patients were randomized into two study groups. The inclusion criteria were as follows; age over 18 years old, HD vintage of at least 3 months as a thrice-weekly schedule, the ability to understand and sign the informed consent, proper performance of arteriovenous fistula or the existing HD catheter, dialysis adequacy (Kt/V) of at least 1.2. The patients were excluded if they had a pregnancy, any active chronic inflammatory disease, uncontrolled or severe, chronic infection or acute infection in recent month, hemoglobin less than 10 g/dL, simultaneous presence in another trial (medical or complementary), the history of medical disease (e.g. myocardial infarction, stroke or surgical) in the last three months, afflicting with the malabsorption syndrome, bleeding disorders (e.g. coagulopathy) or high risk of bleeding, dietary changes in the last month, intolerance or sensitivity to pentoxifylline, receiving the medications affecting inflammatory markers during the recent 6 months, simultaneous consumption of cimetidine, ketorolac, theophylline derivatives and warfarin.

Once included (after obtaining written consent), patients were randomly allocated (using a computer-generated randomization list) to treatment or control groups; the treatment group consisted of 44 patients who received 400 mg pentoxifylline tablet for three months, and the control group consisted of 44 patients who received the matching placebo tablet for three months. Both pentoxifylline and placebo tablets were purchased from Amin Pharmaceutical Company, Isfahan, Iran. The placebo tablets comprised starch and were identical in shape, size, color, and packaging to the pentoxifylline tablets. The compliance of the study patients was tracked by checking each empty blister given back by the patients. Also, there were no serious adverse effects of the drug/placebo the causing patient to withdraw from the study.

At the beginning and end of the study, concentrations of CRP and TNF-α were measured and documented. At the same time, the health-related quality of life (HRQoL) questionnaire on QoL(SF-36) was also completed by each patient in both study groups.

Biochemical measurements

At the baseline and end of the study, 4 ml of blood were obtained from each patient before the initiation of dialysis session. The blood samples were centrifuged at 3000 rpm, then the separated sera transferred to the microtubes. The collected serum samples were kept in the refrigerator of the Central Laboratory at -70°C until the end of the study.

Once the study was finished, the immunoturbidimetry technique (ALCYON 300 at the Drug Applied Research Center of Tabriz University of Medical Sciences) and quantitative diagnostic kit for serum hs-CRP (developed by Pars Azmoon Company, Tehran, Iran) were used to measure the CRP concentration. In this experiment, CRP in the specimens formed a complex with the polyclonal antibodies sensitized against the human CRP, which was encoded on the latex particles and resulted in opacity. The amount of this opacity was directly connected to the CRP concentration in the patient sample. The kit used for measuring the CRP was designed with a limit of detection of 0.1-20 mg/L. In cases where the CRP levels were over 20 mg/L, the samples were diluted with physiological serum in a ratio of 1:1, and the test results were multiplied by 2. ELISA method was used to measure TNF-α which is a solid phase Enzyme Amplified Sensitivity Immunoassay performed on microtiter plate. The assay used monoclonal antibodies directed against distinct epitopes of TNF-α. The kit was produced by German Company of Demeditec (Demeditec Diagnostics GmbH.Lise-Meitner-StraBe2.24145 Kiel (Germany)). After adding the solutions and formation of a sandwich, the amount of substrate

turnover was determined calorimetrically by measuring the absorbance, which is proportional to the TNF-α concentration. A calibration curve was plotted and TNF-α concentration in samples was determined by interpolation from the calibration curve.

Quality of life assessment

To investigate the HRQoL, the SF-36 questionnaire was used. The validity and reliability of its Persian version in Iranian clinical studies have been assessed and confirmed.[14] The SF-36 contains 36 multiple-choice questions (i.e., 2 to 6 choices) categorized into eight general sections. Questions in each section are scored from 0 to 100, the mean score in each part is reported as the total score of that part. Furthermore, three parameters, i.e., overall quality of life, physical component summary (PCS), and mental component summary (MCS), were defined: total QoL is the mean score of all parts; PCS is the means score of physical functioning, limitation due to physical issues, vitality, pain, and health; and MCS is the mean score of parts related to the limitation due to the mental issues, vitality, emotional health, social functioning, and public health. The higher the scores in each part, the better and superior QoLin that part.[15]

Statistical methods

Data were reported as number/percentage or mean ± standard deviation as appropriate based on their type and distribution. To compare quantitative data between groups, the t-test or its non-parametric form Mann-Whitney U Test, was used. The Fisher's exact test or Chi-squared test was used to compare the qualitative parameters between groups. Due to the importance of controlling confounding factors, analysis of covariance was used to adjust the effects of confounding factors such as age, sex, baseline values, dialysis adequacy, and duration of dialysis on the values of the main data at the end of the study. For quantitative data with a non-normal distribution pattern, the bootstrap estimation method with the lowest error rate was used. Statistical analyses were performed by the Statistical Package for Social Sciences (SPSS) version 18. The Statistically significant level was set at $P < 0.05$.

Results

A total of 250 HD patients were screened for eligibility criteria and finally 100 patients entered into the study. Altogether, 12 patients were excluded from the study because of death (4 persons), kidney transplantation (1 person) and unwillingness (7 persons). So, data of excluded patients were not mentioned for final analysis (Figure 1). Finally, 88 patients finished the study (61.4% males and 37.6% females).

Table 1 represents a summary of the patients' baseline demographic characteristics in both study groups.

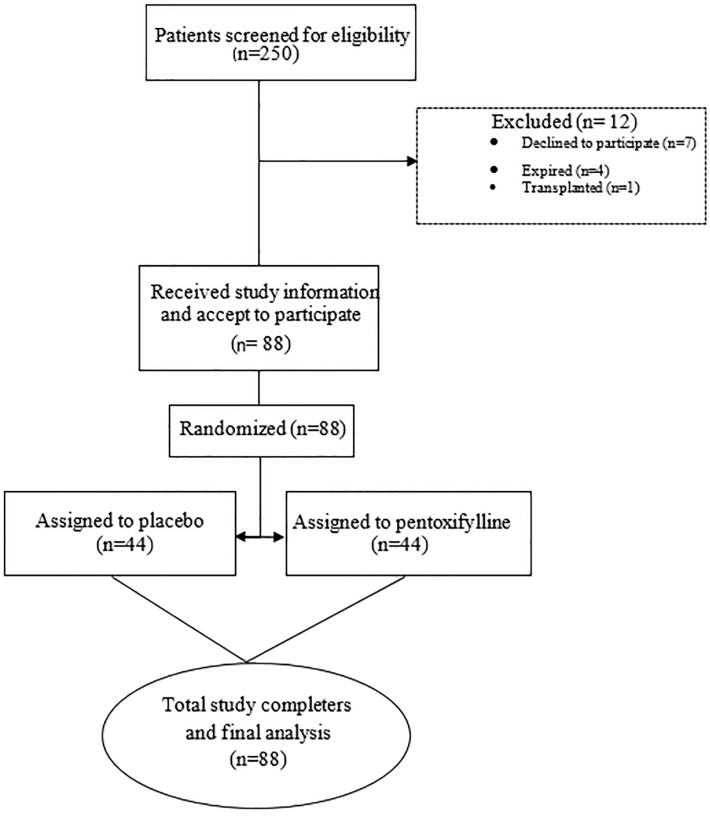

Figure 1. Study's flowchart indicating patients' screening and randomization procedure.

Table 1. Demographic and clinical information of patients at the beginning of the study.

Characteristics		Placebo group (n=44)	Pentoxifylline group (n=44)	P-value
Age (y)		56.81±12.63	60.13±13.73	0.24
Sex	Male	28 (63.6%)	26 (59.1%)	0.66
	Female	16 (36.4%)	18 (40.9%)	
Marital	Married	38 (86.4%)	42 (95.5%)	0.13
	Single	6 (13.6%)	2 (4.5%)	
Underlying disease	DM	12 (27.3%)	7 (15.9%)	0.50
	HTN	16 (36.4%)	16 (36.4%)	
	DM-HTN	10 (22.7%)	11 (25%)	
Others		6 (13.6%)	10 (22.7%)	
Dialysis adequacy		1.39±0.29	1.28±0.23	0.06
Months on dialysis		50.13±26.84	56.63±31.54	0.30

DM: Diabetes mellitus; HTN: Hypertension; DM-HTN: diabetes mellitus (DM) and Hypertension (HTN).

The mean ages of patients in the pentoxifylline and placebo groups were 60.13±13.73 and 56.81±12.63 years, respectively. There were no statistically significant differences between the two groups in terms of age, gender, marital status, underlying disease, dialysis adequacy, and dialysis duration.

As shown in Table 2, there was no significant difference in CRP level between placebo and pentoxifylline groups at the baseline. During the study, CRP level decreased in the pentoxifylline group significantly (P < 0.001) without any significant changes in the placebo group (P = 0.84). However, no significant difference was seen in the patients' CRP level at the end of the study between two groups (P = 0.14). TNF-α level was significantly different between placebo and pentoxifylline groups at the beginning of study (P < 0.001). During the study period, TNF-α level in pentoxifylline group decreased significantly (P = 0.04), but no difference was observed in the placebo group (P = 0.07). The patients' TNF-α level was significantly different between two groups at the end of the study (P < 0.001).

Additionally, results showed that there was no significant difference between the various dimensions of QoL in both groups at the beginning of the study (Table 3). Once the study ended, all dimensions of QoL in the pentoxifylline group were significantly improved ($P < 0.05$), while the changes in the placebo group were significant only for "vitality" dimension ($P = 0.02$). However, at the end of the study, various dimensions of QoL showed no significant difference between the study groups.

Altogether, at the end of the study, the values of the variables including CRP ($P = 0.14$), PCS ($P = 0.91$), MCS ($P = 0.7$), and overall QoL score ($P = 0.82$) in the pentoxifylline group were not significantly different from those in the placebo group.

After adjusting the values of each variable for their confounding factors including baseline values, gender, age, dialysis adequacy and dialysis duration, a considerable decrease was indicated in the variables of CRP and TNF-α in pentoxifylline group compared to placebo group ($P < 0.05$), also a significant improvement in the variables of PCS, MCS and overall QoL score was observed in the pentoxifylline group compared to placebo group ($P < 0.05$) (Table 3).

The relationship between changes in inflammatory markers (TNF-α, CRP) with overall QoL score and the physical component of QoL as well as the mental component of QoL was also assessed. However, there was no relationship between changes in inflammatory factors in the pentoxifylline and placebo groups with the general parameters of QoL (Table 4).

Discussion

The current study was performed to investigate the potential effect of pentoxifylline on inflammatory factors and QoL in HD patients. We found that TNF-α and CRP values, after adjusting for their baseline values, gender, age, dialysis adequacy and duration, markedly decreased in pentoxifylline group compared to the placebo group.

Table 2. Comparing the serum level of the studied inflammatory factors.

	Placebo group (n=44)			Pentoxifylline group (n=44)			P†	p¥
	Baseline	After 3months	P*	Baseline	After 3 months	P*		
CRP	15.12±9.01	14.88±9.57	0.84	19.99±11.81	11.71±7.29	P<0.001	0.14	.003
TNF-α	36.53±15.02	41.21±20.42	0.07	21.3±10.05	17.09±14.97	0.04	P<0.001	.003

Data are expressed as mean±SD.
*Pertaining to within-group comparison.
†Pertaining to between-group comparison at the end of the study.
¥ Pertaining to between-group comparison after adjusting the level of variables for their baselines, gender, age, dialysis adequacy and dialysis duration.

Table 3. Comparing the different dimensions of patients' quality of life.

Components of quality of life	Placebo (n=44)			Pentoxifylline (n=44)			P†	p¥
	Baseline	After 3 month	P*	Baseline	After 3 month	P*		
Physical functioning	42.84±20.86	42.95±21.78	0.83	39.88±25.55	42.15±25.97	P<0.001	0.87	
Role physical	44.31±43.42	45.45±39.72	0.79	28.40±41.96	42.61±40.19	0.003	0.74	
Role emotional	56.96±44.46	62.12±39.76	0.28	46.96±48.92	56.81±46.9	0.005	0.56	
Vitality	43.29±13.97	44.09±14.11	0.02	41.02±14.12	42.38±14.07	0.009	0.57	
Mental health	52.06±16.29	51.95±16.33	0.69	57.06±14.42	58.93±14.44	P<0.001	0.07	
Social functioning	61.64±20.60	61.93±19.43	0.71	64.77±19.11	67.04±17.9	0.04	0.2	
Bodily pain	58.18±25.43	58.97±23.88	0.70	56.98±27.06	64.77±23.39	P<0.001	0.25	
General health	38.45±15.19	38.45±15.19	1.0	38.86±14.74	40.22±14.09	0.002	0.57	
PCS	45.41±17.71	45.98±17.44	0.62	41.03±19.78	46.43±19.66	P<0.001	0.91	0.003
MCS	50.48±16.29	51.7±16.48	0.23	49.73±18.97	53.08±17.86	P<0.001	0.7	0.027
Overall score	49.72±16.69	50.74±16.92	0.35	46.74±19.74	51.61±18.92	P<0.001	0.82	0.002

Data are expressed as mean±SD.
*Pertaining to within-group comparison.
†Pertaining to between-group comparison at the end of the study.
¥ Pertaining to between-group comparison after adjusting the level of variables for their baselines, gender, age, dialysis adequacy and dialysis duration.

In addition, different dimensions of quality of life, after adjusting the final values for baseline values, gender, age, dialysis adequacy, and duration illustrated significant improvement, particularly in the mental and physical components as well as overall QoL in the pentoxifylline group. In the placebo group, the changes in variables of QoL were not significant, except for the vitality component. There are several tools to assess HRQoL; some of them with generic application and some with disease specific use. The generic HRQoL tools are used in general population and patients with different disease types. SF-36 is one of the frequently used generic types.[16] Examples of HRQoL questionnaires specific for ESRD patients include Kidney Disease QoL Short Form (KDQOL-SF),[17] QoL Index-Dialysis (QLI-D),[18] and Renal QoL Profile (RQLP).[19] A good correlation between RQLP, as a HD-specific HRQoL survey, and SF-36 has been reported previously.[20] Further, validation of the Persian version of the SF-36 has been performed in Iranian patients, and Iranian psychologists/psychiatrists widely use this questionnaire in their practice. Additionally, the SF-36 questionnaire has been used by other researchers in HD patients as well.[21] Hence, we used the SF-36 instrument to assess HRQoL in our patients. HD patients are known to have poor quality of life.[22] In 2001, Mittal *et al.*[21] showed that chronic HD is associated with more impaired QoL than many other chronic disease conditions, including angina pectoris, rheumatoid arthritis, chronic obstructive pulmonary diseases, and heart failure. In the Dialysis Outcomes and Practice Patterns Study (DOPSS), as a large study on dialysis patients' HRQoL, QoL was regarded as a strong predictor of mortality and hospitalization.[23] Thus, new therapeutic modalities are urgently needed to improve HRQoL in chronic HD patients. Although strategies such as frequent HD, 5–6 times weekly as short daily or nocturnal dialysis, rather than conventional thrice weekly HD have been promising for ameliorating QoL and prolonging patient's survival,[24] but they have not been adequate to obviate the need for other therapeutic approaches. Interestingly, findings of our study showed that physical and mental components as well as overall HRQoL significantly improved in chronic HD patients after daily administration of 400 mg pentoxifylline for 3 months. We found no studies on the potential effects of pentoxifylline in this patient population's HRQoL

Table 4. Correlation between the changes of inflammatory markers and quality of life.

		Pentoxifylline		Placebo	
		CRP changes	TNF-α changes	CRP changes	TNF-α changes
Total QoL changes	**Correlation Coefficient**	0.057	-0.165	-0.082	-0.056
	p-value	0.715	0.296	0.598	0.716
MSC changes	**Correlation Coefficient**	-0.233	0.093	0.098	0.009
	p-value	0.128	0.558	0.526	0.953
PCS changes	**Correlation Coefficient**	0.112	-0.248	-0.038	-0.061
	p-value	0.468	0.114	0.807	0.694

in available literature to compare our results and there was no direct data for comparison, but in other studies, pentoxifylline has shown its effectiveness for other diseases conditions. In the study by Mehrzad *et al.*,[25] it was shown that the use of 400 mg of pentoxifylline 3 times a day for 2 months significantly improved QoL of patients with cancer. In another study, the authors investigated the impact of pentoxifylline on QoLin patients with restless legs syndrome. 80 diabetic patients were assessed in two treatment and control groups. In the treatment group, use of 400 mg of pentoxifylline 3 times a day for 8 months improved the quality of life, particularly in the dimensions associated with mental problems and physical health.

Due to the larger sample size and longer duration of patient follow-up, we claim that our study complements all the studies done previously. This is also the first and only available study to investigate the effect of pentoxifylline in HD patients and the correlation between serum levels of inflammatory factors and QoL after consumption of pentoxifylline. High compliance of patients and restricting patient's selection by eliminating patients with glomerulonephritis and renal cysts that affect the amount of inflammatory factors, reinforces the results of our study. Among the uremic rats, treatment with pentoxifylline prevented the increase in serum concentration of inflammatory factors and markers of oxidative stress resulting from the excessive use of sodium.[26] In the study by Navarro *et al.*,[27] the daily use of 400 mg of pentoxifylline for 6 months among 14 diabetic patients with advanced kidney failure reduced effectively the proteinuria and serum concentration of TNF-α, while no significant difference was seen among 10 patients in control group. González-Espinoza *et al.*[28] stated that pentoxifylline can be a promising and suitable strategy for reducing systemic inflammation, which is mostly seen among HD patients. Their study conducted on 36 HD patients in two groups, demonstrating that the daily use of 400 mg of pentoxifylline for 4 months reduced significantly the serum concentration of TNF-α, IL-6 and CRP, while their values were remained constant or increased in the placebo group.[26] The findings of their study were consistent with the present study. In another study, 54 HD patients evaluated in Zahedan, Iran. Results showed that daily use of 400 mg of pentoxifylline for 4 months significantly reduced serum CRP levels, but this reduction was not significant in the placebo group.[19] Another study was conducted on the impact of pentoxifylline on CRP serum level and also the dialysis adequacy by Soltani *et al.*[3] In this study, 73 HD patients were included in two treatment and control groups (39 and 34 patients, respectively). There was no significant difference in CRP value between them at the beginning of the study. CRP levels increased after 1 month of daily usage of 400 mg of pentoxifylline in the treatment group, but this rise was not significant. This was because CRP levels in the placebo group had dramatically increased. The difference between this study and the current study may be due to the short study time and limited sample size. In line with these studies, in a systemic review and meta-analysis conducted by Brie *et al.*[20] on 15 randomized controlled trials, with participants by diverse disorders such as coronary artery disease, type 2 diabetes mellitus, idiopathic and ischemic cardiomyopathy and chronic kidney disease meta-analysis showed a significant effect of pentoxifylline treatment in reducing plasma concentrations of TNF-α and CRP concentrations.The recent study by Sedaghattalab *et al.*[29] investigated the effect of pentoxifylline on the inflammatory cytokines, dialysis adequacy, anemia, and biochemical markers of HD patients. In this study, 42 individuals were selected and divided into control and treatment groups. The treatment group received 400 mg of pentoxifylline for 3 months. The control group received no special drug. Results showed that as the treatment group used the pentoxifylline, level of TNF-α and CPR decreased significantly, but the amount of these changes was not significant compared to the control group and this results led to the uncertainty in conclusion.[27]

The current study had some limitations precluding exact conclusions that pentoxifylline has a substantial impact on improving QoL in HD patients. Instead, studies with larger sample size and longer duration are needed to find more decisive results. We propose more research on pleiotropic effects of pentoxifylline in HD patients with particular attention on its various anti-inflammatory effects.

Conclusion

Pentoxifylline had a significant effect on reducing the serum level of TNF-α and CRP. Pentoxifylline was also highly effective in improving QoL of HD patients in various dimensions, with significant improvements in psychosocial, physical, and overall quality of life. However, changes in various aspect of QoL did not significantly correlate with changes in serum levels of TNF-α and CRP.

Ethical Issues

The protocol of the study was approval by the ethics committee of the Tabriz University of Medical Sciences with the code number of IR.TBZMED.REC.1397.954. This study has also been registered at Iranian registry of clinical trials with registration number of IRCT20170609034406N3. Each enrolled patient signed an informed consent form.

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Data Sharing

Data would be available upon request from corresponding author.

Author Contributions

Lachin Rezadoost: Investigation, Writing - Original Draft.

Hamid Tayebi-Khosroshahi: Conceptualization, Review & Editing. Farahnoosh Farnood: Investigation, Writing - Review & Editing. Parvin Sarbakhsh: Formal Analysis, Writing - Review & Editing. Hossein Behzad: Investigation, Writing - Review & Editing. Hamid Noshad: Investigation, Writing - Review & Editing. Afshin Gharekhani: Conceptualization, Methodology, Writing - Original Draft.

Conflict of Interest

There was no conflict of interest.

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