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ORIGINAL ARTICLE

Effect of Pentoxifylline on Inflammatory Cytokines, Adequacy of Dialysis, Anemia and Biochemical Markers of Hemodialysis Patients: a Randomized Controlled Trial

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SUMMARY

Background: **The main cause of death in hemodialysis patients is cardiovascular disease (CVD). Chronic inflammation is strongly related with CVD, atherosclerosis, and malnutrition in end-stage renal disease (ESRD) patients. We aimed to investigate the effect of pentoxifylline on adequacy of dialysis, anemia, inflammatory cytokines, and biochemical markers in patients with ESRD on hemodialysis.**

Methods: **This was a randomized controlled trial with a negative result conducted on 42 hemodialysis patients. The patients were randomly divided to two groups; intervention group (400 mg pentoxifylline every night for three months) and control group (followed up without taking pentoxifylline). The blood samples were taken to measure the levels of inflammatory cytokines, anemia-related parameters, and biochemical markers at baseline and the end of treatment.**

Results: **Thirty-six patients finished the study (18 patients in each group). There was significant reduction in C-reactive protein (CRP) [9.25 (4.60, 17.62) vs. 5.60 (1.90, 11.52), p = 0.048] and TNF-α [28.06 (19.76, 61.22) vs. 18.06 (14.39, 28.97), p = 0.029], and significant increase of albumin levels (4.05 ± 0.25 vs. 4.35 ± 0.24, p = 0.000) in the intervention group, but these changes were not significant in comparison with the control group. No statistically significant difference was observed between intervention and control groups in other parameters.**

Conclusions: **Although pentoxifylline administration had caused significant reduction in CRP and TNF-α, as well as significant increase of albumin levels in the intervention group, but these changes were not significant in comparison with control group. The current study does not support the use of pentoxifylline in hemodialysis patients.**
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KEY WORDS

pentoxifylline, inflammatory markers, adequacy of dialysis, anemia, hemodialysis

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem. Approximately 15% to 20% of CKD patients may be at risk of loss of kidney function over time. CKD is an important risk factor for end-stage renal dis-

ease (ESRD) [1]. The mortality rate of ESRD patients is significantly higher than normal population as a result of cardiovascular diseases (CVDs). In other words, CVD is the main cause of death in dialysis patients [2]. CKD patients have shown markedly higher C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) levels in serum. Higher levels of TNF-α and IL-6 are associated with higher albuminuria and lower estimated glomerular filtration rate (eGFR) [3]. Chronic inflammation is strongly related with CVD, atherosclerosis, and malnutrition in ESRD patients [4]. Acute phase markers, such as CRP, TNF-α, and IL-6, are predictors for CVDs in patients with chronic renal failure [5]. The inflammatory response is mediated with some cytokines, especially IL-6 and TNF-α; augmentation of these markers are associated with increase of CVD in individuals with normal renal function [6]. Pentoxifylline, a derivative of methylxanthine and inhibitor of phosphodiesterase, has immunomodulatory and anti-inflammatory properties [7]. This drug reduces mortality and morbidity in premature neonates with sepsis, necrotizing enterocolitis and chronic lung disease [8]. Pentoxifylline is effective in alcoholic liver disease and can improve short-term survival in patients with severe alcoholic hepatitis [9]. Pentoxifylline has been studied as a probable CKD treatment; animal models showed that pentoxifylline attenuated renal disease progression [10,11]. Also, clinical trial studies have shown that pentoxifylline improves renal function (glomerular filtration rate), diminishes proteinuria, and reduces TNF-α serum level [7,12]. In a study conducted recently on hemodialysis patients, pentoxifylline led to reduction in pro-inflammatory factors, such as IL-6, TNF-α, and CRP [4]. Moreover, administration of pentoxifylline leads to an insignificant improvement in adequacy of dialysis [13] and a significant attenuation of CRP level [14] as compared to placebo group. Pentoxifylline improved hemoglobin levels in CKD patients with erythropoietin-resistant anemia [15,16]. On the other hand, Mortazavi et al. showed no significant difference in hemoglobin and serum albumin in ESRD patients after treatment with pentoxifylline [17].

According to limiting clinical trials, conflicting results and using small sample sizes [4,13-17], we aimed to investigate the effect of pentoxifylline on adequacy of dialysis, anemia, inflammatory cytokines, and biochemical markers in patients with ESRD on hemodialysis.

MATERIALS AND METHODS

This was a randomized, controlled trial study conducted in Shahid Beheshti Hospital of Yasuj University of Medical Sciences between October 2017 and March 2018. From the whole group of hemodialysis patients, 42 patients were selected using simple random sampling. Inclusion criteria were ≥ 18 years, ≥ 3 months on hemodialysis, and three times a week hemodialysis. Exclusion criteria were as follows: 1) hepatic disease, malignancy, AIDS, rheumatic diseases and other inflammatory diseases; 2) presence of infection in the last two months; 3) rejected renal transplantation; 4) allergy to pentoxifylline and other methylxanthines; 5) active infectious disease during the study; 6) pre-existing cardiac arrhythmias; 7) hypotension; 8) taking antibiotics, NSAIDs (nonsteroidal anti-inflammatory drugs) and steroidal anti-inflammatory drugs; 8) immunodeficiency; 9) taking pentoxifylline in recent three months; 10) patient's displeasure to continue the study; and 11) kidney transplantation.

After registering and verifying the present study with the research committee of Yasuj University of Medical Sciences and obtaining an Ethical code (IR.YUMS.REC.1396.85), registered in Iranian Clinical Trial System (www.irct.ir) with registration number of IRCT 20150622022869N6. Initially, the project and its goals were explained to patients. Then, they were included in the study after obtaining informed consent. They were able to leave the study freely. All patients were interviewed, medical history and physical examinations were taken, consumed drugs and demographic characteristics were recorded. The participants and the investigators were blinded throughout the trial. The patients were randomly (with 1:1 ratio) divided to two groups of intervention and control. During a three months' period, the patients in the intervention group took 400 mg pentoxifylline oral tablets once a day (at dinner time), and those in control group were followed up without taking pentoxifylline. Pentoxifylline dose was selected according to previous clinical and pharmacologic studies [7, 18]. At the end of each month, the patients were visited and evaluated clinically. In each visit, the presence of any infection was rule out. The patient's drug box was controlled for presence of confounding medications, such as NSAIDs or corticosteroids. The patients were monitored to detect drug side effects based on the dialysis frequency of at least three times a week. The patient's compliance with treatment was recorded by counting the remaining tablets in each package during the visit.

A 5 mL blood sample was taken (when dialysis catheter was attached to the patient) at baseline and the end of treatment for measurement of complete blood count, glucose, triglycerides (TG), cholesterol (Cho), albumin, calcium (Ca), phosphorus (P), uric acid, ferritin, serum iron, total iron binding capacity (TIBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine (Cr), and hemoglobin A1C (HbA1C) (assayed by usual methods). All of the laboratory evaluations were done with one person in a well-equipped laboratory.

In serum samples, levels of CRP, TNF-α, IL-6 and IL-10 were evaluated using ELISA kits (IBL international GmbH, Hamburg, Germany). Lower detection limit was 5 pg/mL for TNF-α, 0.92 pg/mL for IL-6, 0.02 µg/mL for CRP and 1.0 pg/mL for IL-10. The inter- and intra-assay variations were 6.13 and 5.1% for CRP, 5.2 and

3.4% for IL-6, 8.1 and 7.7% for TNF-α, 5.6 and 3.2% for IL-10, respectively.

Adequacy of dialysis was done according to measuring the pre- and post-dialysis urea using the method of reducing pump round per minute (rpm) and then stopping it [19]. In dialysis adequacy formula with kinetic urea method (KT/V), V = the urea dispersion volume in liters, T = duration of dialysis session (in hours), and K = dialysis clearance or clearance of the plasma by filter (liter per hour). The parameter K is dependent on some other parameters, such as dialysis filter, the value of blood flow, and the value of dialysis flow. The ratio of KT/V was calculated using following formula [13]:

KT/V = -Ln (R - 0.008*T) + (4 - 3.5*R) * UF/W

In which,

R = pre-dialysis urea/post-dialysis urea,

UF = ultrafiltration value (pre-dialysis weight - post-dialysis weight)

W = post-dialysis weight

T = time

Statistical analysis

Results are presented as mean ± SD or median (25th to 75th interquartile range). The normality was determined to select the proper statistical test. Baseline variables were evaluated to determine the probable significant intergroup changes. An independent *t*-test and paired *t*-test were utilized for parametric distributions. The Mann-Whitney U test and Wilcoxon signed-rank test were utilized for nonparametric distributed variables. The significance level was assumed as $p < 0.05$.

RESULTS

The flow diagram of this randomized clinical trial is shown in Figure 1. Out of 42 hemodialysis patients, 21 patients entered each group (21 patients in the intervention group and 21 patients in the control group). Among the patients of the intervention group, two patients left the study due to intolerance of pentoxifylline (nausea and vomiting) and one patient quit due to change of hemodialysis into peritoneal dialysis. In the control group two patients were also lost due to death (caused by cerebrovascular accident and myocardial infarction) and one patient left the study due to heart valve replacement surgery. Finally, 18 patients in the intervention group (11 males and 7 females) and 18 patients in the control group (11 males and 7 females) completed the study. In the current study, the main cause of renal failure was diabetes in 16 (44.44%), hypertension in 13 (36.11%), glomerulonephritis in 3 (8.33%), and unknown in 4 (11.11%) patients.

Baseline characteristics

Baseline data of the patients are detailed in Table 1. The baseline variable showed that there was no significant change among the variables between intervention and control groups.

Effects of pentoxifylline on inflammatory cytokines

Differences between the two groups based on measured inflammatory markers at the end of the study are presented in Table 2. There was significant reduction in CRP [9.25 (4.60, 17.62) vs. 5.60 (1.90, 11.52), $p = 0.048$] and TNF-α [28.06 (19.76, 61.22) vs. 18.06 (14.39, 28.97), $p = 0.029$] in the intervention group, but these changes were not significant in comparison with the control group (Figure 2A - B). No statistically significant difference was observed between the intervention and control group in interleukin 6 ($p = 0.364$) and interleukin 10 ($p = 0.373$) levels.

Effects of pentoxifylline on adequacy of dialysis and anemia

Table 3 shows comparisons of adequacy of dialysis and anemia-related variables between groups at the beginning and the end of the study. There were no significant changes between groups concerning ferritin, serum iron, TIBC, hemoglobin and PLT. Alteration in adequacy of dialysis level was not significantly different between the two groups.

Effects of pentoxifylline on biochemical parameters

Table 3 shows the metabolic and anthropometric parameters of the participants at baseline and after 3 months of pentoxifylline or without taking pentoxifylline (control). There were no significant changes in the mean serum Ca, P, Cho, and TG levels between the intervention and control groups. Variations in serum glucose and HbA1C levels were not markedly different between the two groups. No significant changes in BUN, Cr, ALT, AST, ALP, and uric acid levels were observed between pentoxifylline and control groups. There was a significant increase of albumin levels (4.05 ± 0.25 vs. 4.35 ± 0.24, $p = 0.000$) in the intervention group, but these changes were not significant in comparison with the control group (Figure 2C).

DISCUSSION

Chronic kidney disease is associated with a progressive decline in GFR. ESRD is a stage of CKD (GFR < 15) where the accumulation of electrolytes, fluid, and toxins leads to death [20]. Cardiovascular risk initiates in the primary stages of CKDs [21]. Approximately 20% of the mortality may be related to coronary artery disease (CAD), while the rest is a result of other types of CVD, such as atrial fibrillation, congestive heart failure, left ventricular (LV) hypertrophy, and valvular heart disease [22]. The major risk factors for CVDs such as dyslipidemia, anemia, chronic inflammation, diabetes, obesity, hyperparathyroidism, hyperhomocysteinemia, uremia, and oxidative stress are common in patients with CKD [20,22].

Inflammatory cytokines, such as hsCRP and IL-6, independently anticipate mortality in CKD patients. The reasons of inflammation in CKD are complicated and com-

Table 1. Baseline characteristics of control and pentoxifylline groups.

Variable	Control	Pentoxifylline	p-value
Age	56.44 ± 18.18	62.72 ± 15.28	0.280
Gender (female/male)	7/11	7/11	1
BMI (kg/m^2)	24.56 ± 3.54	25.10 ± 4.69	0.700
CRP (µg/mL)	9.75 ± 8.70	16.35 ± 18.35	0.177
IL-6 (pg/mL)	16.48 ± 37.44	7.75 ± 8.48	0.341
IL-10 (pg/mL)	26.75 ± 19.18	22.41 ± 12.95	0.432
TNF-α (pg/mL)	25.21 ± 18.15	39.81 ± 2919	0.080
Albumin (g/dL)	4.04 ± 0.25	4.05 ± 0.25	0.949
Ca (mg/dL)	8.80 ± 0.54	8.53 ± 0.70	0.220
P (mg/dL)	5.43 ± 1.38	5.27 ± 1.35	0.726
TG (mg/dL)	129.83 ± 72.89	129.27 ± 60.13	0.980
Cho (mg/dL)	137.83 ± 39.01	134.00 ± 39.22	0.771
Ferritin (mcg/dL)	445.05 ± 606.64	402.05 ± 413.96	0.805
Serum iron (mcg/dL)	77.72 ± 23.86	63.66 ± 17.85	0.053
TIBC (mcg/dL)	259.61 ± 57.12	275.55 ± 63.37	0.453
Hemoglobin (g/dL)	11.16 ± 1.23	11.41 ± 1.52	0.585
PLT (1,000 x mm^3)	174,166.66 ± 74,790.88	174,722.22 ± 53,288.12	0.980
BUN (mg/dL)	53.00 ± 14.34	51.83 ± 16.67	0.823
Cr (mg/dL)	7.80 (5.15, 9.39)	8.17 (4.79, 9.20)	0.887
Glucose (mg/dL)	109.50 (88.50, 121.50)	96.00 (83.50, 144.00)	0.837
HbA1C (%)	6.86 ± 1.15	6.75 ± 1.32	0.866
ALT (IU/L)	15.83 ± 9.30	14.44 ± 6.24	0.602
AST (IU/L)	15.50 (11.00, 19.00)	12.00 (9.50, 17.50)	0.303
ALP (IU/L)	364.44 ± 253.07	454.16 ± 299.66	0.339
Uric acid	7.01 ± 1.55	7.16 ± 1.89	0.796
KT/V	1.07 ± 0.27	1.16 ± 0.28	0.382
Access (AVF/Catheter)	15/3	12/6	0.255
Duration of dialysis (months)	26.16 ± 20.12	24.27 ± 15.26	0.753
Erythropoietin dose (unit/week)	4,888.88 ± 3,197.22	5,388.88 ± 5,042.62	0.725

Values are mean ± SD for data with normal distribution and median (interquartile ranges) for data not normally distributed.
BMI - body mass index, CRP - C-reactive protein, IL-6 - interleukin-6, IL-10 - interleukin-10, TNF-α - tumor necrosis factor-α, Ca - calcium, P - phosphorus, TG - triglycerides, Cho - cholesterol, TIBC - total iron binding capacity, HbA1c - glycated hemoglobin, BUN - blood urea nitrogen, Cr - creatinine, AST - aspartate aminotransferase, ALT - alanine aminotransferase, ALP - alkaline phosphatase, PLT - platelet, KT/V - adequacy of dialysis, AVF - arteriovenous fistula.

prise inequality between enlarged production (due to oxidative stress, infections and the dialysis process) and insufficient removal (due to inadequate dialytic clearance or reduced GFR) of pro-inflammatory biomarkers [23].

Pentoxifylline has been effective in reducing the inflammatory markers of hemodialysis patients [4], and it is promising to say that we can reduce the risk of CVD in these patients via reducing inflammation. Gonzalez-Espinoza et al. found that administration of 400 mg pentoxifylline for 4 months in hemodialysis patients caused a reduction in inflammatory markers, including TNF-α, IL-6 and CRP [4]. Also, Alidadi and Golabchi-Fard showed that 400 mg pentoxifylline for 4 months significantly decreased serum levels of CRP compared to placebo [14]. However, Soltani et al. observed that administration of pentoxifylline (400 mg for 1 month) was not associated with significant reduction in the CRP level [13]. Pentoxifylline has anti-inflammatory activity by reducing synthesis of pro-inflammatory markers, inhibiting proliferation of peripheral blood mononuclear cells, and preventing synthesis of the in-

Table 2. Comparison of changes in the inflammatory markers during the study period between the control and pentoxifylline groups.

Variable	Baseline	After 3 months	p-value	% change	p-value
CRP (µg/mL)					
Control	**7.50 (4.60, 11.62)**	**5.15 (1.85, 9.30)**	**0.022**	**-2.45 (-5.20, -0.12)**	**0.849**
Pentoxifylline	**9.25 (4.60, 17.62)**	**5.60 (1.90, 11.52)**	**0.048**	**-2.80 (-11.60, 1.25)**	
IL-6 (pg/mL)					
Control	**7.44 (1.36, 14.13)**	**3.75 (0.98, 12.08)**	**0.215**	**-0.85 (-5.15, 2.21)**	**0.364**
Pentoxifylline	**4.79 (1.36, 12.65)**	**5.55 (0.95, 13.92)**	**0.528**	**0.36 (-3.64, 6.68)**	
IL-10 (pg/mL)					
Control	**26.75±19.18**	**23.20 (13.45, 28.87)**	**0.446**	**-3.96 ± 20.39**	**0.373**
Pentoxifylline	**22.41±12.95**	**25.15 (16.66, 29.84)**	**0.913**	**1.95 ± 18.89**	
TNF-α (pg/mL)					
Control	**20.11 (13.91, 34.24)**	**14.54 (10.89, 27.02)**	**0.184**	**-4.74 ± 18.22**	**0.164**
Pentoxifylline	**28.06 (19.76, 61.22)**	**18.06 (14.39, 28.97)**	**0.029**	**-14.69 ± 23.44**	

Values are mean ± SD for data with normal distribution and median (interquartile ranges) for data not normally distributed.
CRP - C-reactive protein, IL-6 - interleukin-6, IL-10 - interleukin-10, TNF-α - tumor necrosis factor-α.

Table 3. Comparison of differences in biochemical parameters during the study between the control and pentoxifylline groups.

Variable	Baseline	After 3 months	p-value	% change	p-value
Albumin (g/dL)					
Control	**4.04 ± 0.25**	**4.27 ± 0.40**	**0.015**	**0.20 (0.10, 0.52)**	**0.911**
Pentoxifylline	**4.05 ± 0.25**	**4.35 ± 0.24**	**0.000**	**0.30 (0.17, 0.42)**	
Ca (mg/dL)					
Control	**8.80 ± 0.54**	**8.61 ± 0.81**	**0.468**	**-0.18 ± 1.08**	**0.362**
Pentoxifylline	**8.53 ± 0.70**	**8.69 ± 0.80**	**0.575**	**0.15 ± 1.15**	
P (mg/dL)					
Control	**5.43 ± 1.38**	**5.39 ± 1.20**	**0.892**	**-0.03 ± 1.20**	**0.780**
Pentoxifylline	**5.27 ± 1.35**	**5.11 ± 1.64**	**0.631**	**-0.16 ± 1.39**	
TG (mg/dL)					
Control	**129.83 ± 72.89**	**140.33 ± 97.42**	**0.333**	**10.50 ± 44.74**	**0.322**
Pentoxifylline	**129.27 ± 60.13**	**125.66 ± 68.04**	**0.701**	**-3.61 ± 39.26**	
Cho (mg/dL)					
Control	**137.83 ± 39.01**	**114.72 ± 28.82**	**0.001**	**-23.11 ± 24.56**	**0.308**
Pentoxifylline	**134.00 ± 39.22**	**122.33 ± 35.04**	**0.232**	**-11.66 ± 39.94**	
Ferritin (mcg/dL)					
Control	**445.05 ± 606.64**	**355.05 ± 276.89**	**0.376**	**-90.00 ± 419.93**	**0.824**
Pentoxifylline	**402.05 ± 413.96**	**338.38 ± 283.38**	**0.329**	**-63.66 ± 268.51**	
Serum iron (mcg/dL)					
Control	**77.72 ± 23.86**	**74.88 ± 24.48**	**0.694**	**-2.83 ± 30.00**	**0.947**
Pentoxifylline	**63.66 ± 17.85**	**60.22 ± 24.67**	**0.555**	**-3.44 ± 24.28**	
TIBC (mcg/dL)					
Control	**259.61 ± 57.12**	**268.11 ± 54.14**	**0.504**	**8.50 ± 52.76**	**0.133**
Pentoxifylline	**275.55 ± 63.37**	**259.72 ± 52.97**	**0.122**	**-15.83 ± 41.28**	

Table 3. Comparison of differences in biochemical parameters during the study between the control and pentoxifylline groups (continued).

Variable	Baseline	After 3 months	p-value	% change	p-value
Hemoglobin (g/dL)					
Control	**11.16 ± 1.23**	**10.87 ± 1.66**	**0.370**	**-0.28 ± 1.30**	**0.437**
Pentoxifylline	**11.41 ± 1.52**	**10.63 ± 1.46**	**0.174**	**-0.77 ± 2.32**	
PLT (1,000 x mm^3)					
Control	**174,166.66 ± 74,790.88**	**172,888.88 ± 72,663.51**	**0.789**	**1,500 (-16,250, 11,250)**	**0.987**
Pentoxifylline	**174,722.22 ± 53,288.12**	**171,777.77 ± 52,438.82**	**0.747**	**-6,000 (-15,250, 16,250)**	
BUN (mg/dL)					
Control	**53.00 ± 14.34**	**51.38 ± 18.13**	**0.516**	**-1.61 ± 10.30**	**0.966**
Pentoxifylline	**51.83 ± 16.67**	**50.44 ± 17.19**	**0.762**	**-1.38 ± 19.16**	
Cr (mg/dL)					
Control	**7.80 (5.15, 9.39)**	**7.16 (4.88, 9.12)**	**0.231**	**-0.26 (-0.96, 0.32)**	**0.764**
Pentoxifylline	**8.17 (4.79, 9.20)**	**7.40 (4.88, 8.84)**	**0.286**	**-0.46 (-1.55, 0.98)**	
Glucose (mg/dL)					
Control	**109.50 (88.50, 121.50)**	**103.00 (89.75, 135.75)**	**0.349**	**0.00 (-6.25, 21.75)**	**0.304**
Pentoxifylline	**96.00 (83.50, 144.00)**	**91.50 (83.75, 131.50)**	**0.513**	**-4.50 (-26.50, 11.75)**	
HbA1C (%)					
Control	**6.86 ± 1.15**	**7.67 ± 1.36**	**0.221**	**0.27 ± 0.86**	**0.351**
Pentoxifylline	**6.75 ± 1.32**	**7.77 ± 1.24**	**0.24**	**0.56 ± 1.00**	
ALT (IU/L)					
Control	**15.83 ± 9.30**	**18.00 ± 13.42**	**0.311**	**2.16 ± 8.80**	**0.560**
Pentoxifylline	**14.44 ± 6.24**	**20.44 ± 25.00**	**0.344**	**6.00 ± 26.17**	
AST (IU/L)					
Control	**15.50 (11.00, 19.00)**	**13.00 (9.00, 17.25)**	**0.082**	**-2.50 ± 5.86**	**0.149**
Pentoxifylline	**12.00 (9.50, 17.50)**	**10.00 (9.00, 15.75)**	**0.295**	**4.05 ± 17.88**	
ALP (IU/L)					
Control	**364.44 ± 253.07**	**336.88 ± 215.13**	**0.106**	**-27.55 ± 68.56**	**0.191**
Pentoxifylline	**454.16 ± 299.66**	**480.94 ± 338.90**	**0.483**	**26.77 ± 158.58**	
Uric acid					
Control	**7.01 ± 1.55**	**6.51 ± 1.20**	**0.157**	**-0.49 ± 1.41**	**0.908**
Pentoxifylline	**7.16 ± 1.89**	**6.60 ± 1.47**	**0.246**	**-0.56 ± 1.97**	
KT/V					
Control	**1.07 ± 0.27**	**1.09 ± 0.22**	**0.744**	**0.02 ± 0.26**	**0.944**
Pentoxifylline	**1.16 ± .0.28**	**1.18 ± 0.32**	**0.733**	**0.02 ± 0.34**	

Values are mean ± SD for data with normal distribution and median (interquartile ranges) for data not normally distributed.
Ca - calcium, P - phosphorus, TG - triacylglycerol, Cho - cholesterol, TIBC - total iron binding capacity, HbA1c - glycated hemoglobin, BUN - blood urea nitrogen, Cr - creatinine, AST - aspartate aminotransferase, ALT - alanine aminotransferase, ALP - alkaline phosphatase, PLT - Platelet, KT/V - adequacy of dialysis.

flammatory cytokines at a transcriptional level [4].
In this study, as it can be inferred from the results, CRP and TNF-α (as positive phase reactants) were significantly reduced in the pentoxifylline (400 mg for 3 months) group, and albumin (as a negative acute-phase reactants) significantly increased, but these changes were not significant in comparison to the control group. We can conclude that the insignificant difference of inflammatory cytokines between the intervention and control groups in our study may be the result of duration of

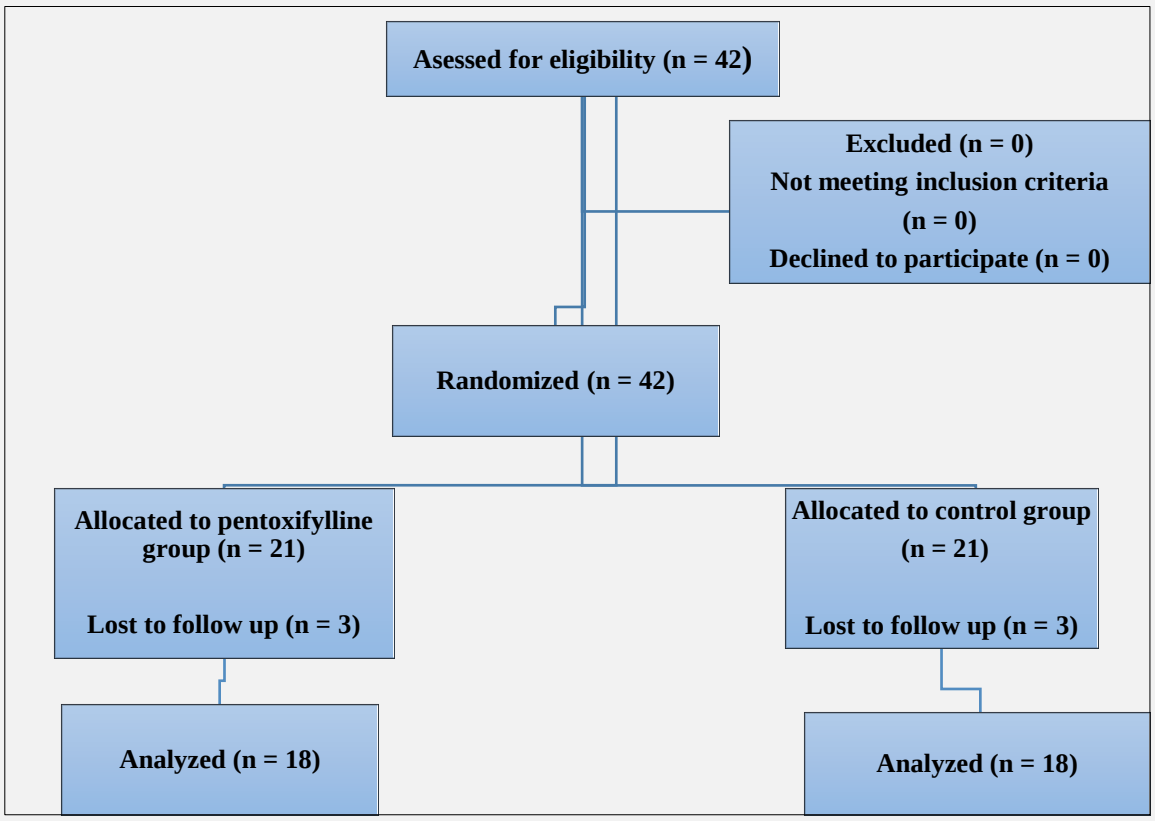

Figure 1. Schematic flow diagram of the study.

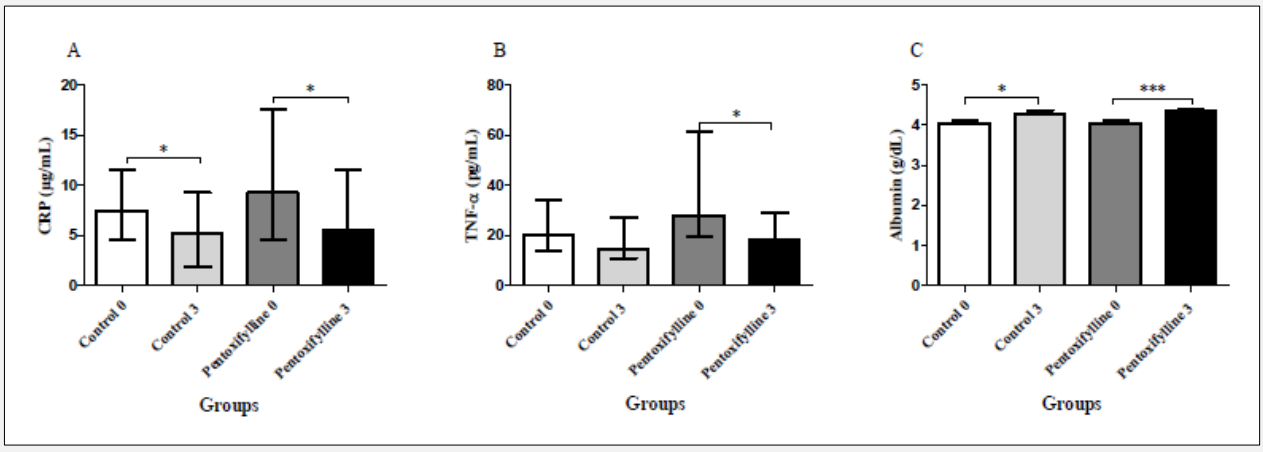

Figure 2. CRP: C-reactive protein, TNF-α: tumor necrosis factor-α and albumin in study population.

(A) CRP, (B) TNF-α, and (C) albumin in pentoxifylline and control groups at baseline (0) and the end of treatment (3). * Statistically significant as p < 0.001, * Statistically significant as p < 0.05.**

pentoxifylline administration, small sample size, and variation in study type. In addition, insignificant changes of albumin in comparison with the control group may be due to good nutrition and adequate hemodialysis of our patients.

Although, previous studies showed that pentoxifylline increases IL-10 level in murine peritoneal macrophages and coronary artery disease [24,25], the current study was the first clinical trial that showed pentoxifylline had no effect on IL-10 in the hemodialysis patients.

Pro-inflammatory cytokines such as interferon-γ and TNF-α may exacerbate anemia by inhibiting the pro-erythropoietic effect of erythropoietin and reducing iron accessibility. Pentoxifylline may improve anemia in CKD by preventing the release of interferon-γ and TNF-α from T-cells and monocytes [26]. Mohammadpour et al. showed that 3 months of treatment with 400 mg pentoxifylline significantly increased Hb in recombinant human erythropoietin-resistant patients [27]. Also, Johnson et al. demonstrated that administration of pentoxifylline augmented Hb after 4 months in hemodialysis patients [28]. In contrast to these studies, Mortazavi et al. did not show a significant change in Hb level of chronic hemodialysis patients after treatment with 400 mg pentoxifylline for 6 months [17]. Our data showed that pentoxifylline has no positive effects on Hb levels in hemodialysis patients; consistent with our results, in a pooled meta-analysis of 7 controlled studies, pentoxifylline did not yield significant differences on Hb levels when compared with placebo or standard therapy [26]. Soltani et al., in their study on 73 hemodialysis patients, concluded that pentoxifylline led to substantial improvement of adequacy of hemodialysis; however, this effect was not statistically significant as compared to the control group [13]. In agreement with this study, we did not find a significant change in adequacy of hemodialysis between pentoxifylline and control groups. We controlled many variables relating to the hemodialysis method, which could have an effect on the results. In this study pentoxifylline had no considerable complications, though we observed nausea in two patients. The present study had some limitations including small sample size, short-term follow-up period, selection patients from one institute, and the existence of concealed infections (Helicobacter pylori and chronic periodontal disease) as a source of inflammation.

CONCLUSION

Administration of pentoxifylline in hemodialysis patients has no significant complications. Although pentoxifylline administration had caused significant reduction in CRP and TNF-α and significant increase of albumin levels, but these changes were not statistically significant in comparison with the control group. Despite the usefulness of pentoxifylline on some inflammatory markers in the pentoxifylline group, the current study does not support the use of pentoxifylline in hemodialysis patients.

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Declaration of Interest:
The authors have declared that no conflict of interest exists.

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