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EFFECT OF PENTOXIFYLLINE ON SERUM CRP LEVELS IN HEMODIALYSIS PATIENTS COMPARED WITH PLACEBO

Ali Alidadi and Reza Golabchi Fard *

Department of Nephrology, Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran.

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Correspondence to Author:
Reza Golabchi Fard

Faculty of Medicine,
Zahedan University of Medical Sciences, Zahedan, Iran.

E-mail: tahghighatt1@gmail.com

ABSTRACT: Introduction: Inflammation indicates with increased levels of inflammatory markers such as CRP is common in hemodialysis patients. Higher levels of CRP is strong predictor of morbidity and mortality in dialysis patients. The aim of this study was to evaluate the effect of pentoxifylline on serum CRP levels in hemodialysis patients compared with placebo. **Methods:** In this randomized clinical trial, 54 patients undergoing hemodialysis were evaluated at Zahedan's hospitals in 1393 year. Patients were randomly divided into two groups receiving pentoxifylline and placebo. CRP Levels in Patients at months zero, two and four were tested. At the end, the data were analyzed with the software SPSS Ver. 20 and Wilcoxon and chi-square test. **Results:** The mean age of patients was 45.9 ± 14.8 years, 25 (46.3%) of the patients were male and 29 (53.7%) were female. CRP levels Before the intervention in patients receiving pentoxifylline was 4.5 ± 4.0, two months after the intervention was 2.8 ± 1.6 and four months after the was 2.3 ± 1.3. (P=0.001) CRP levels before the intervention in patients receiving placebo was 5.8 ± 5.6, two months after the intervention was 4.9 ± 3.8 and four months after was 5.1 ± 4.1. (P>0.05)The CRP differences in patients receiving pentoxifylline before and after intervention was 2.2 ± 3.7 and in patients receiving placebo was 0.7 ± 5.3 (P=0.035). **Conclusion:** Pentoxifylline significantly decreased serum concentrations of CRP compared to placebo. Pentoxifylline could be a promising and useful strategy to reduce the systemic inflammation frequently observed in patients on hemodialysis.

INTRODUCTION: Chronic kidney disease (CKD), a disorder in which kidneys cannot keep the blood pressure, urea level and fluid and acid-base in the normal range, progresses over time and results in renal failure, the last stage of which is called end-stage renal disease (ESRD) needing a renal replacement therapy such as dialysis or transplantation. In Iran, there are nearly 15000 ESRD patients and a half of them are receiving hemodialysis [1, 2, 3]. ESRD patients cannot maintain the balance between pro-inflammatory cytokines and their inhibitors.

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This imbalance, along with the dialysis process and exposure to endotoxins and cytokines, results in a highly prevalent state of persistent inflammation in these patients [4, 5, 6, 7]. The chronic inflammation decreases the quality of life and dialysis adequacy and causes a poor response to erythropoietin in anaemia, which is highly prevalent in ESRD patients [3, 8]. C-reactive protein (CRP), an acute phase protein, is increased in inflammatory processes such a hemodialysis and so it is used for evaluation the degree of inflammation [8]. It has been shown that pentoxifylline, a methylxantine-derived phosphodiesterase inhibitor, reduces the systemic inflammation by decreasing the expression of tumor necrosis factor alpha (TNF-a), interleukin (IL)-1b, IL-6 and IL-8 and by increasing IL-10 [9, 10]. A few studies have investigated the effect of pentoxifylline on CRP level in hemodialysis patients.

In the Gonza´lez-Espinoza *et al*., 2011 study pentoxifylline, compared to the placebo, could significantly decrease the serum levels of TNF-a, IL-6 and CRP [11]. Soltani *et al*., (2016), however, could not show any significant reduction in the CRP level with pentoxifylline, although it could prevent the significant increase in CRP [8]. There is not enough evidence to certainly conclude about the effect of pentoxifylline on inflammatory markers in hemodialysis patients. Therefore, the aim of this study was to investigate the pentoxifylline effect on serum level of CRP in hemodialysis patients.

MATERIALS AND METHODS: This double-blind placebo-controlled randomized clinical trial was conducted between September 2014 and January 2016 on hemodialysis patients in Ali-ebne-Abi-Taleb hospital, Zahedan, Iran. Hemodialysis patients aged 18 -70 years with at least 2 month of history of hemodialysis were included in this study. Exclusion criteria were having active hepatic disease, active or chronic infection and allergy to pentoxifylline, bleeding disorders, hypotension and using non-steroidal anti-inflammatory drugs (NSAIDs). All patients were undergoing hemodialysis 3 times a week, 4 h each time. Using a computer-generated randomization list, patients were randomly assigned into 2 equal groups; pentoxifylline group, receiving 400 mg oral pentoxifylline (SR, Farabi, Tehran, Iran) once daily, and placebo group. All patients and investigators were blinded to the group assignment. Serum CRP levels were measured at baseline and 2 and 4 months later for both groups. The measurements were performed by the same person in the central laboratory of Ali-ebne-Abi-Taleb hospital, Zahedan, Iran.

This study was approved by the ethics committee of Zahedan University of Medical Sciences and it was registered in the Iranian Registry of Clinical Trials under the code 48882395. All patients provided informed written consent. SPSSv20.0 software (Statistical Package for Social Sciences, Chicago, IL) was used for data analysis. Data were compared using Student's t-test or Mann-Whitney test. $P<0.05$ was considered statistically significant.

RESULTS: In this study 54 hemodialysis patients, 29 (53.7 %) females and 25 males (46.3 %) with a mean age of 45.9 ± 14.8 years, were evaluated **Table 1**. In pentoxifylline group, CRP level at baseline was 4.5 ± 4.0mg/L. The difference between CRP level at baseline and at 2 months and also between baseline and 4 months was statistically significant (P=0.001; **Table 2**).

TABLE 1: PARTICIPANTS'CHARACTERISTICS

	Sex		Age
	Male (%)	Female (%)	(years)
Pentoxifylline group	11 (40.7)	16 (59.3)	44.3 ±15.0
Placebo Group	14 (51.9)	13 (48.1)	47.4 ±14.7
P value	0.413		0.435

TABLE 2: SERUM CRP LEVELS OF THE PARTICIPANTS AT DIFFERENT TIME POINTS

		CRP (mg/L)	P value
Pentoxifylline group	Baseline	4.5 ± 4.0	0.001
	2 Months	2.8 ± 1.6	
	4 Months	2.3 ± 1.3	
Placebo group	Baseline	5.8 ± 5.6	0.421
	2 Months	4.9 ± 3.8	
	4 Months	5.1 ± 4.1	

Baseline CRP level in placebo group was 5.8 ± 5.6 mg/L and its level at 2 months and 4 months was 4.9 ± 3.8 mg/L and 5.1 ± 4.1mg/L, respectively, but the difference between these levels was not significant (P = 0.421; **Table 2**). The difference between the baseline and 4 months CRP level in the pentoxifylline group was 2.2 ± 3.7 mg/L; this difference in the placebo group was 0.7 ± 1.5 mg/L **Table 3**.

TABLE 3: COMPARISON THE DIFFERENCE OF SERUM CRP LEVELS BETWEEN STUDY GROUPS

		CRP (mg/L)	Baseline and 4 month difference	P value
Pentoxifylline group	Baseline	4.5 ± 4.0	2.2 ± 3.7	0.035
	4 months	2.3 ± 1.3		
Placebo group	Baseline	5.8 ± 5.6	0.7 ± 1.5	
	4 months	5.1 ± 4.1		

DISCUSSION: In the current study a 4-month trial of pentoxifylline caused a significant decrease in CRP level; in placebo group CRP level was also decreased but it was not significant. In the Goicoechea *et al*., study on the effects of pentoxifylline on inflammatory parameters in chronic kidney disease patients it was shown that pentoxifylline could significantly decrease the serum level of tumor necrosis factor-alpha (TNF-α) and high-sensitivity C-reactive protein (hs-CRP) [12]. In another study by L. Gonza´lez-Espinoza *et al*., the serum level of inflammatory biomarkers, CRP, TNF-α and interleukin 6 (IL-6), was

significantly decreased after using pentoxifylline for four months [11]. Soltani and his colleagues in their study on 73 ESRD patients on hemodialysis showed that at the end of study, serum CRP level in the placebo group increased significantly; in pentoxifylline group it was also increased but not significantly. In another words, pentoxifylline could not decrease the CRP level compared to baseline. This is not consistent with the results of the current study; this inconsistency may be explained by the different follow-up durations in these two studies.

We followed the patients for a 4 month period but the follow up duration in their study was only 1 month [8]. Pentoxifylline, by inhibiting phospho-diesterase, increases intracellular cyclic adenosine monophosphate activity and down-regulates the synthesis of pro-inflammatory cytokines such as TNF-a, IL-6 and interferon-c [9]. Hemodialysis patients suffer a highly inflammatory condition; thus reducing the inflammation can slow the progression of renal disease and improve the adequacy of the dialysis and more importantly the quality of life of the patient [7, 8].

Soltani *et al*., showed that using pentoxifylline in end stage renal disease patients undergoing maintenance hemodialysis causes a significant improvement in dialysis adequacy [8]. Juan F. Navarro-González *et al*., showed that in stages 3 - 4 CKD patients receiving standard medical care, pentoxifylline slows the progression rate of nephropathy [13]. Persistent inflammation in hemodialysis patients results in an erythropoietin-resistant anaemia [14]. TNF-α plays an important role in the pathogenesis of anaemia resulting from inflammation [15]. Pentoxifylline, by decreasing serum TNF-α in the serum of renal failure patients, can probably increase the hemoglobin level and thus improve the anaemia [14].

Mohammadpour *et al*., conducted a trial on 15 hemodialysis patients. After 3 months of using pentoxifylline, they observed a significant increase in hemoglobin in 8 patients (53%; good responders) with erythropoietin-resistant anaemia; There was also a significant inverse correlation between serum TNF-α concentration and haemoglobin level in this good responders group [14]. This study investigated the effect of pentoxifylline on the serum level of only one inflammatory biomarker, CRP, in hemodialysis patients. Further studies with larger sample size can investigate the effect of pentoxifylline on other inflammatory biomarkers such as TNF-α, IL-6 and CRP concurrently; these studies should also evaluate whether reduction in inflammation is associated with improvement in the quality of life of the patients, response to erythropoietin in erythropoietin-resistant anaemia patients and also whether it can reduce or even stop the renal disease progression.

In conclusion, in this study pentoxifylline could significantly decrease the serum level of CRP in hemodialysis patients; this reduction in the pentoxifylline group was significantly higher than placebo group.

CONCLUSION: Pentoxifylline significantly decreased serum concentrations of CRP compared to placebo. Pentoxifylline could be a promising and useful strategy to reduce the systemic inflammation frequently observed in patients on hemodialysis.

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