A Randomized Clinical Trial of the Effect of Pentoxifylline on C-Reactive Protein Level and Dialysis Adequacy in End-stage Renal Disease Patients on Maintenance Hemodialysis

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Introduction. C-reactive protein (CRP) is increased among patients on maintenance hemodialysis. Such inflammatory markers can result in protein-energy deficit syndromes and low adequacy of dialysis in these patients. This study evaluated the effect of pentoxifylline on serum CRP level and KT/V in end-stage renal disease patients on maintenance hemodialysis.

Material and Methods. This 1-month randomized, double-blind, placebo-controlled clinical trial involving 73 patients with end-stage renal disease on maintenance hemodialysis assessed the effectiveness of 400 mg/d of pentoxifylline on serum CRP level decrease and improvement of dialysis adequacy.

Results. The difference in mean serum CRP levels of the pentoxifylline and placebo groups was not significant before study. While CRP showed showed a significant increase in the placebo group after completing the interventions (P = .01), the difference was nonsignificant in the pentoxifylline group (P = .53). The difference in the mean adequacy of dialysis was not significant before the interventions between the two groups, while there was a significant increase in the pentoxifylline group (P = .01) and a nonsignificant increase in the placebo group (P = .31) after the interventions.

Conclusions. Among patients on maintenance hemodialysis, a 1-month trial of pentoxifylline was associated with a substantial improvement of adequacy of dialysis and a significant prevention from serum CRP level increase, but not a significant reduction in the mean serum CRP level.

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INTRODUCTION

In the immune system, a complex orchestration of cytokines and other molecules act in a paracrine, autocrine, or endocrine fashion to control the differentiation, proliferation, and activity of immune cells. As the kidney is the major site for elimination of many cytokines, the delicate equilibrium of pro-inflammatory cytokines and their inhibitors is clearly deregulated in end-stage renal disease (ESRD) patients.[1,2] The consequences of the altered immune response in uremia and dialysis process lead to a major exposure to cytokines and endotoxins,[3-5] and a state of persistent inflammation,[6,7] which is highly prevalent among ESRD patients and is linked to complications such as the development of protein-energy wasting and atherosclerotic vascular disease.[8] C-reactive protein (CRP) is one the most traditional cytokines studied among ESRD patients. Its increase in inflammatory processes such as dialysis is a known

phenomenon. In clinical practice, the acute phase protein CRP is still the most commonly used biomarker of the degree of inflammation. There are some articles which emphasize on CRP level reduction among hemodialysis patients with a trial of pentoxifylline.[9,10]

There are few studies working on residual renal function, nutritional status, inflammatory environment, or protein intake through intermittent hemodialysis and peritoneal dialysis as some variables with different effects on dialysis adequacy (KT/V) than dialysis alone,[11] based on which patients with residual renal function had a steeper slope in the relationship between KT/V urea and protein catabolic rate. These factors may act solely or in combination and other unknown mechanisms may also be involved. A positive, but weak, linear correlation was observed in protein catabolic rate and KT/V urea in patients with residual renal function.[12]

In this study, we evaluated the effect of pentoxifylline on serum CRP level and KT/V in end-stage renal disease patients on maintenance hemodialysis.

MATERIAL AND METHODS

Study Design

The study was a randomized, double-blind, placebo-controlled clinical trial of 1-month pentoxifylline (400 mg, SR, Farabi, Tehran, Iran) in end-stage renal disease patients on maintenance hemodialysis to evaluate the effect of pentoxifylline on serum CRP level and adequacy of dialysis. The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT2013120715695N1), and approved by the ethics committee (92-148-12) of Arak Medical University. Patients on maintenance hemodialysis at Valiasr Hospital, Arak Medical University, were enrolled in this study after providing informed written consent.

The participants were older than 15 years old and were on maintenance hemodialysis for more than 3 months (3 times a week, 4 hours each). We excluded patients with a history of pentoxifylline or other anti-inflammatory use before this study, abnormal liver function tests, hypersensitivity reaction to pentoxifylline, active infection, recent malignancy, history of depression, recent intracranial hemorrhage, and recent retinal hemorrhage. We followed them up for 1 month to ascertain the outcome of expected decrease in serum CRP level and improvement in dialysis adequacy.

Randomization

Randomization was performed in permuted blocks, stratified according to the placebo and treatment groups. Statistical analyses were performed at the center of Arak Medical University. We randomly assigned patients to receive daily 400 mg of pentoxifylline or placebo (Starch tablets packaging in similar pockets) for 30 days. One staff was responsible for data coordination between the patients and their drug groups without the knowledge of whether the patient receives the medication or the placebo.

Study Procedures

Serum CRP level was measured before and 1 month after the trial therapy by a kit for quantitative CRP (Labor Diagnostika Nord, Nordhorn, Germany). Adequacy of dialysis was assessed before and 1 month after the trial therapy by measuring KT/V as dialysis clearance of urea. This equation was simplified by statistical methods as follows:

Percent of urea reduction ratio = [1 – (postdialysis blood urea nitrogen/predialysis blood urea nitrogen)] × 100

KT/V = (0.026 × percent of urea reduction ratio) - 0.460

Statistical Analysis

We estimated that a sample of 73 patients the two study groups would provide at least 80% power to detect probable reduction in the serum CRP level of patients on maintenance hemodialysis and an improvement in adequacy of dialysis during this 1-month follow-up period. Descriptive and investigational studies were performed for the results. We used the *t* tests, paired *t* test, and the Cox model of treatment effects. A *P* value less than .05 was considered significant.

RESULTS

Study Participants

Capture of screening data commenced in March of 2014. Eighty-two eligible patients were enrolled throughout the study; 42 patients were randomly allocated to pentoxifylline and 40 to placebo. Patients who were withdrawn from the study

were those who discontinued the intervention or patients who developed febrile disease resulting in an increase in acute phase reactants independent to our trial therapy. Finally, 73 patients completed the study (39 patients in the pentoxifylline group and 34 in the placebo group).

Baseline demographic and clinical characteristics of the trial participants are summarized in Table 1. The median age was 60.5 years, the youngest participant was 22 years old, and the oldest one was 86 years old. Forty (54.8%) participants were men. In the pentoxifylline group, 21 patients (53.8%) were men, and in the control group, 19 patients (55.8%) were men. The median dialysis period was 91.24 months.

Serum C-Reactive Protein Level

The mean serum CRP levels in the pentoxifylline and the placebo groups before and 1 month after the interventions are depicted in Table 2. The difference in mean serum CRP levels the two groups was not significant before study (P = .19). The mean serum CRP levels after completing the interventions showed a significant increase in the placebo group (P = .01) and a nonsignificant increase in the pentoxifylline group (P = .53).

Table 1. Baseline Demographic and Clinical Characteristics of Study Groups

Characteristics	Participants Groups		
	Pentoxifylline (n = 39)	Placebo (n = 34)	All (n = 73)
Mean age, y	52.4 ± 1.1	68.6 ± 1.4	60.52 ± 1.6
Sex			
Male	21 (53.8)	19 (55.9)	40 (54.8)
Female	18 (46.1)	15 (44.1)	33 (46.2)
Median time on dialysis, mo	92.18	89.25	91.24

Table 2. Clinical Outcomes of Study Groups

Outcome	Participants Groups		*P*
	Pentoxifylline (n = 39)	Placebo (n = 34)	
C-reactive protein, ng/mL			
Before study	7061	5741	
After study	7190	7678	.19
Before-after *P*	.53	.01	
Dialysis adequacy (KT/V)			
Before study	1.09	1.10	
After study	1.24	1.20	.78
Before-after *P*	.01	.31	

Adequacy of Dialysis

The mean adequacy of dialysis (KT/V) values before and after the interventions are depicted in Table 2. The difference in the mean adequacy of dialysis was not significant before the interventions (P = .78), while there was a significant increase in the pentoxifylline group (P = .01) and a nonsignificant increase in the placebo group (P = .31) after the interventions. These results emphasized on a significant improvement in adequacy of dialysis in the pentoxifylline group.

DISCUSSION

The mean serum CRP levels measured among our study population revealed a severe increase (more than 50 times more than the upper limit of normal, which is 100 ng/mL), indicative of severe risk of cardiovascular diseases in these patients. High levels of serum CRP among patients on maintenance dialysis is an alarm sign presenting the value of this study, which tries to assess an agent which would be effective in lowering of serum CRP level. Serum CRP level in this study was measured in patients on at least 3 months of hemodialysis in order to assess the progress of serum CRP level after receiving placebo or pentoxifylline; therefore we did not need the serum CRP level of each patient before dialysis.

Pentoxifylline treatment in ESRD patients on maintenance dialysis was associated with a significant improvement in adequacy of dialysis and an effective prevention from expected increase of serum CRP level. Significant increases in serum CRP level were seen in the placebo group after 1 month, emphasizing the expected increase of serum CRP level during dialysis period. Alongside the study, we tried to exclude patients with severe malaise and febrile diseases like catheter-related infections and urinary tract infection, to eliminate the interferential reasons of serum CRP increase. Differences between the drug and placebo groups were apparent after 1 month of trial and would be better to be followed and rechecked for months after the end of the trial therapy. It is also logical to carry out more studies in different groups of patients, in different parts of the world, with longer time of trial therapy. Our trial therapy was only 1 month, and it is probable that a longer intervention therapy would be accompanied by more decreases in serum CRP level with pentoxifylline and greater

improvement in adequacy of dialysis. Our study had certain limitations; for example, the population of this study was only from 1 institute and may not be applicable to patients with different demographics or clinical characteristics and locations, and the access of dialysis would be effective on dialysis adequacy. There were several confounding factors which could interfere with serum CRP level, such as our patients' primary diseases leading to ESRD, comorbidities, and using other supplements, and medications. We randomized the patients and excluded patients with new-onset malaise resulting in fluctuations in serum CRP level.

There are both similarities and differences between our findings and those of other trials. Goicoechea and colleagues[9] showed that pentoxifylline is a potential therapeutic agent in chronic kidney disease due to its anti-inflammatory and antiproteinuric effects that may influence the progression of kidney disease. In their randomized trial of 91 patients with chronic kidney disease, high-sensitivity CRP, serum fibrinogen, and tumor necrosis factor-α decreased significantly in those treated with pentoxifylline in comparison with the control group at 12 months.[9]

González-Espinoza and coworkers[10] compared the effect of pentoxifylline versus placebo on serum concentrations of tumor necrosis factor-α, interleukin-6, and CRP of hemodialysis patients. In a randomized double-blind, controlled trial, hemodialysis patients without infection or drugs with anti-inflammatory effect were randomly allocated to a study or control group; pentoxifylline significantly decreased serum concentrations of tumor necrosis factor-α, interleukin-6, and CRP as compared to those in the placebo group.[10]

Reasons of improvement in adequacy of dialysis are moot point. Dialysis adequacy is dependent on different factors such as types of dialysis access (semipermanent catheters, atrioventricular fistulas, grafts, and temporary catheters) and types of dialysis membranes, which were randomized in this clinical trial. Some studies are emphasizing on the relationships of residual renal function in hemodialysis and peritoneal dialysis and nutritional status and inflammatory markers on adequacy of dialysis.[12] In a cross-sectional study in Fars province, Iran, 632 patients on hemodialysis in 15 dialysis centers were assessed.[13] The KT/V was calculated, and data on serum levels of albumin, cholesterol, and triglyceride, hemoglobin level, blood pressure, body weight, and body mass index were collected. The values were compared with the Kidney Disease Outcomes Quality Initiative recommended target values. Only 32.1% of the patients achieved the KT/V goal. Seventy-four percent of the patients had a serum albumin equal or greater than 4 g/dL. Hemoglobin levels were between 4.6 g/dL and 16.8 g/dL, and half of the patients had attainment of the hemoglobin target. Cholesterol target was reached in 40% of patients. Only 43 patients (6.8%) attained all targets recommended by the guidelines.[13]

There are 137 hemodialysis centers affiliated to 30 medical universities in Iran. In a national study,[14] all demographic data as well as hemodialysis prescription data, including blood flow rate, length of the hemodialysis session, hemodialysis membrane type, and composition of the dialysis solution were recorded for each patient. In addition, urea reduction ratio and KT/V were calculated to determine the hemodialysis adequacy. Bicarbonate-based solutions and low-flux membranes were prescribed for 77.0% and 97.6% of the patients, respectively. The mean blood flow rate was 242.9 ± 39.2 mL/min. The mean length of hemodialysis session was 229.2 ± 22.2 minutes. The mean urea reduction ratio and KT/V were calculated to be 61.0 ± 11.8% and 1.2 ± 0.4, respectively. A KT/V less than 1.2 and a urea reduction ratio less than 65% were found in 56.7%, and 65.2% of the hemodialysis patients, respectively. This study showed a substantially inadequate hemodialysis in Iran as compared with the Kidney Disease Outcomes Quality Initiative guidelines.[14] These two recent studies in Iran show low adequacy of dialysis among Iranian patients on hemodialysis and emphasize the importance of searching new ways to improve adequacy of dialysis among patients on hemodialysis in Iran.

A reduction in inflammatory markers can result in a better appetite, better nutritional status, and an improvement in dialysis adequacy. However, there are not a lot of studies to show and prove these relationships. We hypothesized that with exercise during dialysis, the increase in muscle blood flow and open capillary surface area would increase the flux of urea from the tissue to the vascular compartment resulting in better serum urea clearance and hence improvement in dialysis adequacy.

CONCLUSIONS

In the present study, pentoxifylline treatment in ESRD patients on maintenance dialysis was associated with a significant improve in adequacy of dialysis. However, this is questionable if this improvement is directly related to pentoxifylline treatment as a result of a reduction in blood viscosity which can improve the flux of urea from the tissue to the vascular compartment, or is indirectly related to anti-inflammatory effects of pentoxifylline. More studies are necessary to re-examine anti-inflammatory effects of different drugs on different groups of patients on maintenance hemodialysis to confirm the anti-inflammatory effects of such medications on dialysis adequacy. More studies on pentoxifylline and other blood viscosity lowering agents with longer duration of therapy are necessary to confirm the positive effect of improvement in the flux of urea from the tissue to the vascular compartment on dialysis adequacy.

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CONFLICT OF INTEREST

None declared.

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